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November 10, 2004

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Certified by

Jon W Dudas

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PTO/SB/16 (04-04)
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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Additional inventors are being named on the 1 *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

Synthesis of Quinoline and Quinazoline Kinase Modulators

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages* 285 ☐ CD(s), Number

☐ Drawing(s) *Number of Sheets* ☑ Other (specify) return postcard

☐ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check or money order is enclosed to cover the filing fees.

☑ The Director is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 50-1108

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FILING FEE Amount ($): 160.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☑ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

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Date June 4, 2004

REGISTRATION NO. 48,425 *(if appropriate)*

Docket Number: EX04-047P

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

PROVISIONAL APPLICATION COVER SHEET
Additional Page

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Docket Number EX04-047P

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Number 1 of 1

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PROVISIONAL PATENT APPLICATION

Synthesis of Quinoline and Quinazoline Kinase Modulators

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Synthesis of Quinoline and Quinazoline Kinase Modulators

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This invention relates to synthesis of compounds for modulating protein kinase enzymatic activity for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration and chemoinvasion. Even more specifically, the invention relates to processes for synthesizing quinazolines and quinolines which inhibit, regulate and/or modulate kinase receptor signal transduction pathways related to the changes in cellular activities as mentioned above, as well as processes for formulating the compounds for pharmaceutical purposes.

Summary of Related Art

[0002] Improvements in the specificity of agents used to treat cancer is of considerable interest because of the therapeutic benefits which would be realized if the side effects associated with the administration of these agents could be reduced. Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms.

[0003] Protein kinases are enzymes that catalyze the phosphorylation of proteins, in particular, hydroxy groups on tyrosine, serine and threonine residues of proteins. The consequences of this seemingly simple activity are staggering; cell differentiation and proliferation; i.e., virtually all aspects of cell life in one-way or another depend on protein kinase activity. Furthermore, abnormal protein kinase activity has been related to a host of disorders, ranging from relatively non-life threatening diseases such as psoriasis to extremely virulent diseases such as glioblastoma (brain cancer).

[0004] Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases have an extracellular, a transmembrane, and an intracellular portion, while non-receptor type tyrosine kinases are wholly intracellular.

[0005] Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. In fact, about 20 different subfamilies of receptor-

type tyrosine kinases have been identified. One tyrosine kinase subfamily, designated the HER subfamily, is comprised of EGFR (HER1), HER2, HER3, and HER4. Ligands of this subfamily of receptors identified so far include epithelial growth factor, TGF-alpha, amphiregulin, HB-EGF, betacellulin and heregulin. Another subfamily of these receptor-type tyrosine kinases is the insulin subfamily, which includes INS-R, IGF-IR, and IR-R. The PDGF subfamily includes the PDGF-alpha and beta receptors, CSFIR, c-Kit and FLK-II. Then there is the FLK family, which is comprised of the kinase insert domain receptor (KDR), fetal liver kinase-1 (FLK-1), fetal liver kinase-4 (FLK-4) and the fms-like tyrosine kinase-1 (flt-1). The PDGF and FLK families are usually considered together due to the similarities of the two groups. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., DN&P 7(6): 334-339, 1994, which is hereby incorporated by reference.

[0006] The non-receptor type of tyrosine kinases is also comprised of numerous subfamilies, including Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack, and LIMK. Each of these subfamilies is further sub-divided into varying receptors. For example, the Src subfamily is one of the largest and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr, and Yrk. The Src subfamily of enzymes has been linked to oncogenesis. For a more detailed discussion of the non-receptor type of tyrosine kinases, see Bolen, Oncogene, 8:2025-2031 (1993), which is hereby incorporated by reference.

[0007] Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases. These include, but are not limited to: immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore, both receptor and non-receptor protein kinases are attractive targets for small molecule drug discovery.

[0008] Modulation (particularly inhibition) of cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc Technol 2001 6, 1005-1024), is an attractive goal for development of small-molecule drugs. Anti-angiogenic therapy represents a potentially important approach for the treatment of solid tumors and other diseases associated with dysregulated vascularization, including ischemic

coronary artery disease, diabetic retinopathy, psoriasis and rheumatoid arthritis. As well, cell antiproliferative agents are desirable to slow or stop the growth of tumors.

[0009] Quinolines and quinazolines bearing substitution, for example at the two, four, six and seven positions of their fused ring system have been shown to be particularly attractive targets for kinase inhibition by a number of groups. Conventional quinoline and quinazoline kinase inhibitors typically have fairly simple substitution about the quinoline or quinazoline fused ten-membered ring system, but recently more complex molecules are being disclosed. For example, we have previously disclosed, in U.S. provisional patent applications 60/506,181 and 60/535,377 which are both incorporated by reference herein in their entirety for all purposes, that certain quinolines and quinazolines are particularly well suited as kinase modulators, more particularly inhibitors of for example c-Met, KDR, c-Kit, flt-3, and flt-4. These molecules in some cases are particularly complex and although they can be made via conventional methods, more efficient routes are desirable, especially in a pharmaceutical setting.

[0010] Conventional methods of making quinolines and quinazolines with the aforementioned substitution patterns usually involve linear construction of a quinoline or quinazoline template upon which relatively simple substitutions are appended. With the advent of more complex substitution about such quinolines and quinazolines (*vide supra*), for example side chains containing cyclic and bicyclic systems with multiple functional groups, conventional methods of synthesis become problematic due to the linear or serial reactions used. Indeed, as such molecules become more complex and the utility of such complex groups is realized, the quinoline and quinazoline ring system becomes more of a sub-structure than a main structure of such inhibitors. Thus it is desirable to find more efficient methods of synthesis, particularly convergent syntheses which are an object of this invention.

SUMMARY OF THE INVENTION

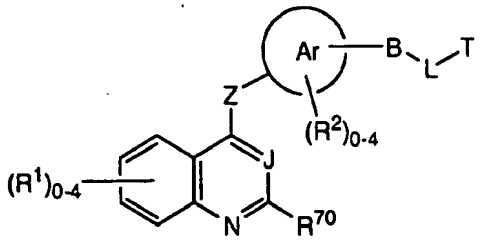
[0011] The present invention provides processes for making compounds, and pharmaceutical compositions thereof, for modulating kinase activity and treating diseases mediated by kinase activity. In particular to this invention are methods for making quinolines and quinazolines used for modulation, even more particularly inhibition, of c-Met, KDR, c-Kit, flt-3, and flt-4,

[0012] These and other features and advantages of the present invention will be described in more detail below with reference to the associated drawings.

DETAILED DESCRIPTION OF THE INVENTION

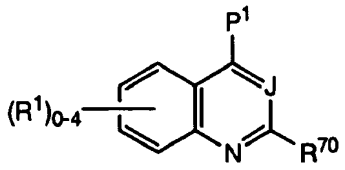
[0013] The methods of the invention are used to make compositions used to treat diseases associated with abnormal and or unregulated cellular activities. Such disease states include, but are not limited to, cancer (further discussed below), immunological disorders such as rheumatoid arthritis, graft-host diseases, multiple sclerosis, psoriasis; cardiovascular diseases such as artheroscrosis, myocardioinfarction, ischemia, stroke and restenosis; other inflammatory and degenerative diseases such as interbowel diseases, osteoarthritus, macular degeneration, diabetic retinopathy.

[0014] The present invention comprises a process for preparing a compound of Formula **I**,

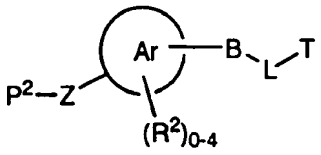


I

comprising reaction of a compound of Formula **II**, with a compound of Formula **III**



II



III

wherein,

each R^1 is independently selected from halogen, $-OR^3$, $-NO_2$, $-NH_2$, $-NR^3R^3$, $-D-R^{50}$ and optionally substituted C_{1-6}alkyl;

R^{70} is selected from -H, halogen, $-OR^3$, $-S(O)_{0-2}R^3$, $-NO_2$, $-NH_2$, $-NR^3R^3$, and optionally substituted C_{1-6}alkyl;

J is selected from =N-, =C(H)-, =C(halogen)-, and =C(CN)-;

Z is selected from $-S(O)_{0-2}$-, -O-, and $-NR^5$-;

R^5 is selected from -H, optionally substituted C_{1-6}alkyl, and optionally substituted aryl C_{1-6}alkyl;

Ar is either a five- or six-membered arylene or a five- or six-membered heteroarylene containing between one and three heteroatoms;

R^2 is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted C_{1-6}alkyl;

B is selected from absent, $-N(R^{13})-$, $-N(SO_2R^{13})-$, -O-, $-S(O)_{0-2}-$, and -C(=O)-;

L is selected from absent, $-C(=S)N(R^{13})-$, $-C(=NR^{14})N(R^{13})-$, $-SO_2N(R^{13})-$, $-SO_2-$, $-C(=O)N(R^{13})-$, $-N(R^{13})-$, $-C(=O)C_{1-2}alkylN(R^{13})-$, $-N(R^{13})C_{1-2}alkylC(=O)-$, $-C(=O)C_{0-1}alkylC(=O)N(R^{13})-$, -C(=O)-, $-C_{0-4}$alkylene-, $-C(=O)C_{0-1}alkylC(=O)OR^3-$, $-C(=NR^{14})C_{0-1}alkylC(=O)-$, $-C(=O)C_{0-1}alkylC(=O)-$, and an optionally substituted four- to six-membered heterocyclyl containing between one and three annular heteroatoms and comprising at least one nitrogen;

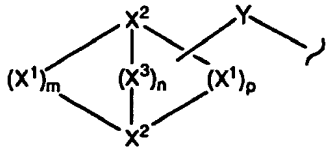
T is selected from -H, $-R^{13}$, $-C_{0-4}$alkyl, $-C_{0-4}alkylQ$, $-OC_{0-4}alkylQ$, $-C_{0-4}alkylOQ$, $-N(R^{13})C_{0-4}alkylQ$, $-SO_2C_{0-4}alkylQ$, $-C(=O)C_{0-4}alkylQ$, $-C_{0-4}alkylN(R^{13})Q$, and $-C(=O)N(R^{13})C_{0-4}alkylQ$, wherein each of the aforementioned C_{0-4}alkyl is optionally substituted;

Q is a five- to ten-membered ring system, optionally substituted with between zero and four of R^{20};

R^{20} is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted C_{1-6}alkyl;

D is selected from -O-, $-S(O)_{0-2}-$, and $-NR^{15}-$;

R^{50} is either R^3, or according to formula **IV**;



IV

wherein X^1, X^2, and optionally X^3, represent the atoms of a saturated bridged ring system, said saturated bridged ring system comprising up to four annular heteroatoms represented by any of X^1, X^2, and X^3; wherein,

each X^1 is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

each X^2 is independently an optionally substituted bridgehead methine or a bridgehead nitrogen;

each X^3 is independently selected from $-C(R^6)R^7-$, -O-, $-S(O)_{0-2}-$, and $-NR^8-$;

Y is either:

an optionally substituted C_{1-6}alkylene linker, between D and either 1) any annular atom of the saturated bridged ring system, except X^2 when X^2 is a bridgehead nitrogen, or 2) any heteroatom, represented by any of R^6 or R^7; provided there are at least two carbon atoms between D and any annular heteroatom of the saturated bridged ring system or any heteroatom represented by any of R^6 or R^7;

or Y is absent, when Y is absent, said saturated bridged ring system, is directly attached to D via an annular carbon of said saturated bridged ring system, unless D is $-SO_2-$, in which case said saturated bridged ring system, is directly attached to D via an any annular atom of said saturated bridged ring system;

m and p are each independently one to four;

n is zero to two, when n is zero, then there is a single bond between the two bridgehead X^2's;

R^6 and R^7 are each independently selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-NCO_2R^3$, $-C(O)R^3$, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, optionally substituted heterocyclyl, optionally substituted heterocyclyl a C_{1-6}lkyl, and a bond to either Y or D; or

R^6 and R^7, when taken together are oxo; or

R^6 and R^7, when taken together with a common carbon to which they are attached, form a optionally substituted three- to seven-membered spirocyclyl, said optionally substituted three- to seven-membered spirocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

R^8 is selected from $-R^3$, Y, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$;

R^{13} is selected from -H, $-C(=O)R^3$, $-C(=O)OR^3$, $-C(=O)SR^3$, $-SO_2R^3$, $-C(=O)N(R^3)R^3$, and optionally substituted C_{1-6}alkyl;

two R^{13}, together with the atom or atoms to which they are attached, can combine to form a heteroalicyclic optionally substituted with between one and four of R^{60}, said heteroalicyclic comprising up to four annular heteroatoms, and said heteroalicyclic optionally comprising an aryl or heteroaryl fused thereto, in which case said aryl or heteroaryl is optionally substituted with an additional one to four of R^{60};

R^{14} is selected from -H, $-NO_2$, $-NH_2$, $-N(R^3)R^3$, -CN, $-OR^3$, optionally substituted C_{1-6}alkyl, optionally substituted heteroalicyclyl C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl and optionally substituted heteroalicyclic;

R^{15} is a group $-M^1-M^2$, wherein M^1 is selected from absent, $-C(=S)N(R^{13})-$, $-C(=NR^{14})N(R^{13})-$, $-SO_2N(R^{13})-$, $-SO_2-$, $-C(=O)N(R^{13})-$, $-C(=O)C(=O)N(R^{13})-$, $-C_{0-4}$alkylene-, -C(=O)-, and an optionally substituted four to six-membered heterocyclyl containing between one and three heteroatoms but comprising at least one nitrogen; and M^2 is selected from -H, $-C_{0-6}$alkyl, alkoxy, $-C(=O)C_{0-4}$alkylQ, $-C_{0-4}$alkylQ, $-OC_{0-4}$alkylQ-, $-N(R^{13})C_{0-4}$alkylQ-, and $-C(=O)N(R^{13})C_{0-4}$alkylQ;

R^{60} is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted heteroaryl C_{1-6}alkyl, and optionally substituted aryl C_{1-6}alkyl;

two of R^{60}, when attached to a non-aromatic carbon, can be oxo;

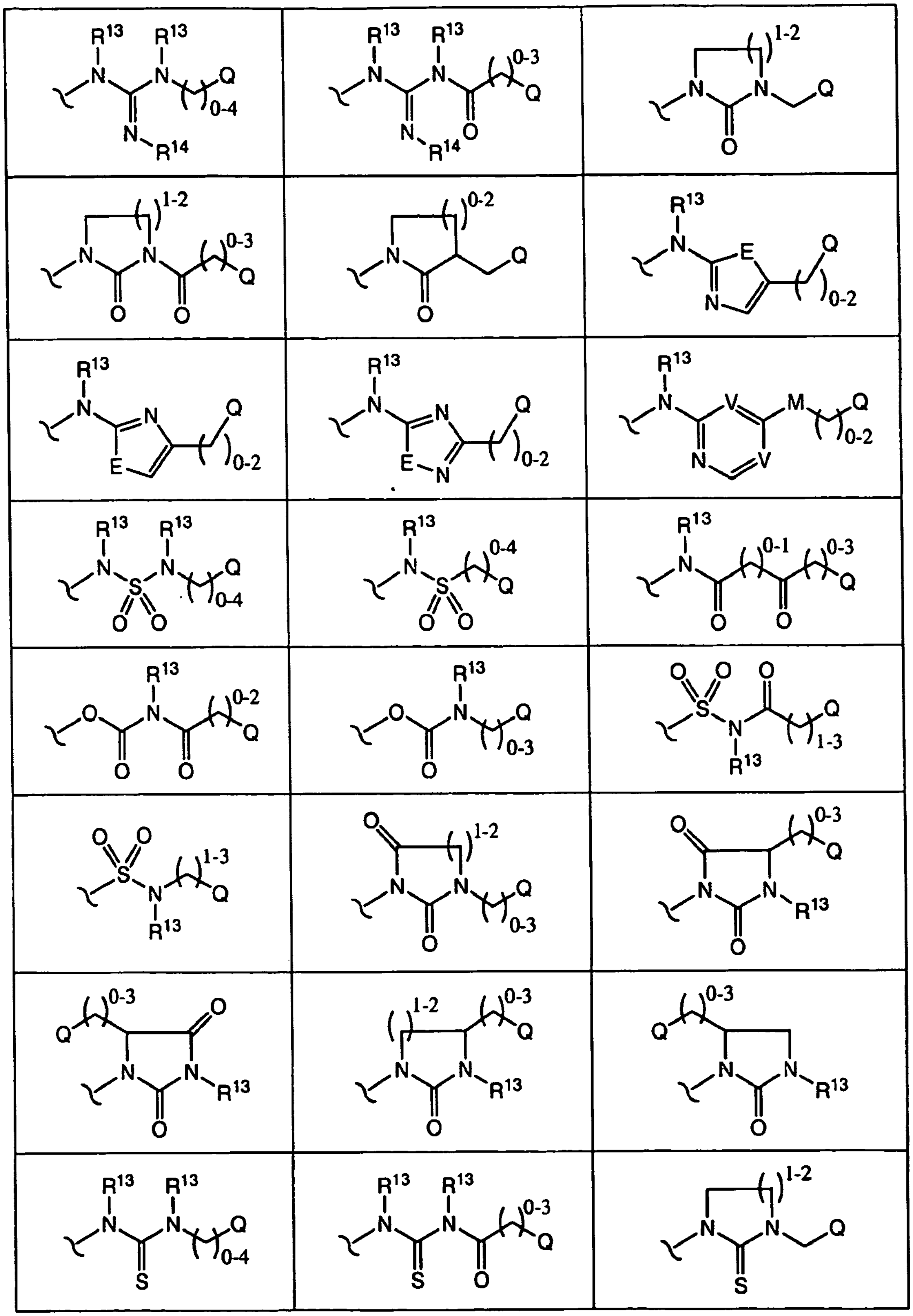
P^1 is a suitable leaving group; and

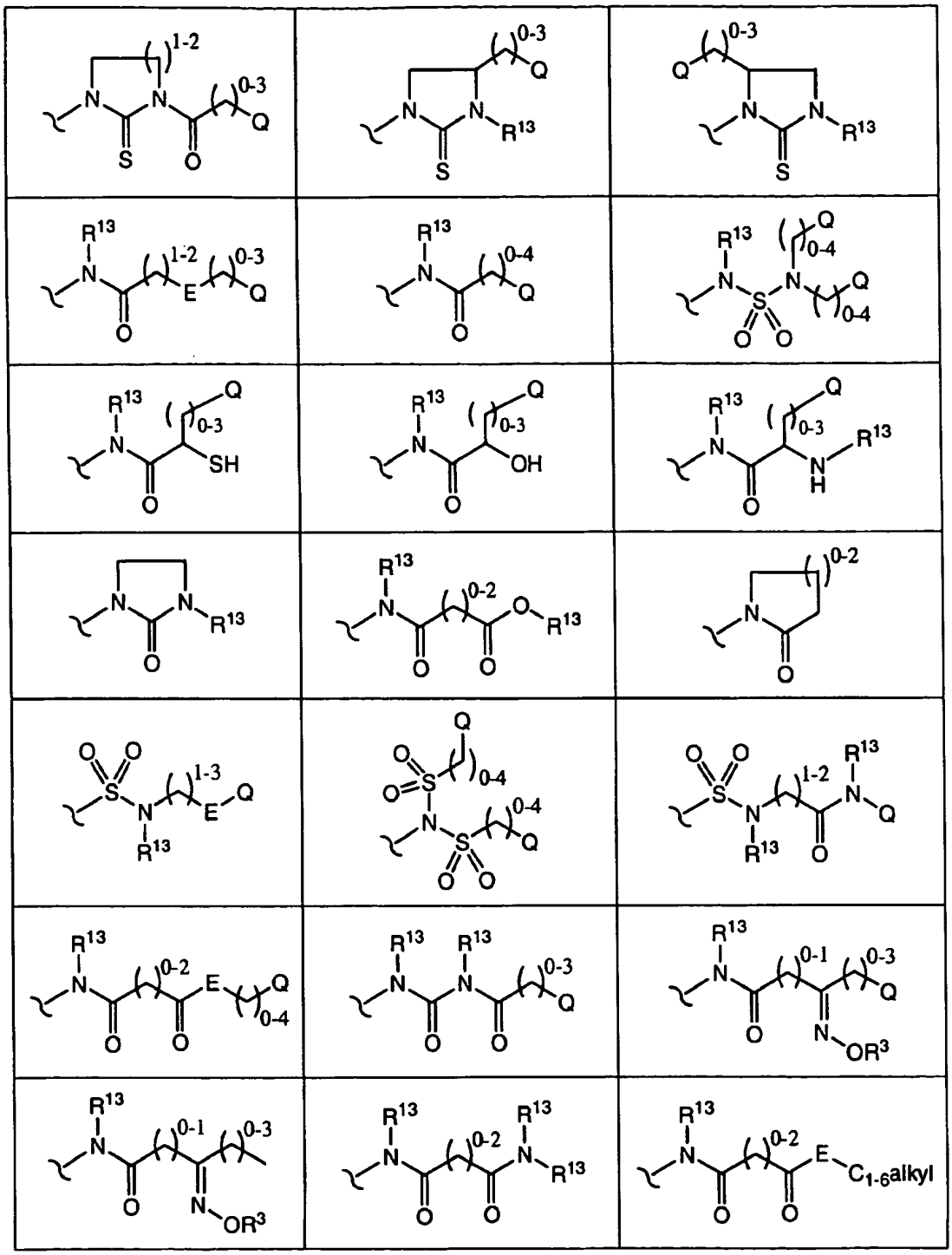
P^2 is selected from -H, a metal, and a group removed *in-situ* when combining **II** and **III** to make **I**.

[0015] In one example, the process is according to paragraph [0014], wherein Ar is *para*-phenylene as defined by the substitution pattern of -Z- and -B-L-T.

[0016] In another example, the process is according to paragraph [0015], wherein Z is either -O- or $-NR^5-$.

[0017] In another example, the process is according to paragraph [0016], wherein -B-L-T is selected from the following:





wherein Q, R^{20}, and R^{13} are as defined above; each E is selected from -O-, -N(R^{13})-, -CH_2-, and -S(O)$_{0-2}$-; M is selected from -O-, -N(R^{13})-, -CH_2-, and -C(=O)N(R^{13})-; each V is independently either =N- or =C(H)-; each methylene in any of the above formulae is independently optionally substituted with R^{25}; and R^{25} is selected from halogen, trihalomethyl, -CN, -NO_2, -NH_2, -OR^3, -NR^3R^3, -S(O)$_{0-2}R^3$, -$SO_2NR^3R^3$, -CO_2R^3,

$-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, heteroaryl C_{1-6}alkyl, and optionally substituted C_{1-6}alkyl; two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form an optionally substituted three- to seven-membered alicyclic or heteroalicyclic; two of R^{25} on a single carbon can be oxo.

[0018] In another example, the process is according to paragraph [0017], wherein there are only two of R^1, one of R^1 is $-D-R^{50}$ and the other R^1 is $-OR^{3a}$.

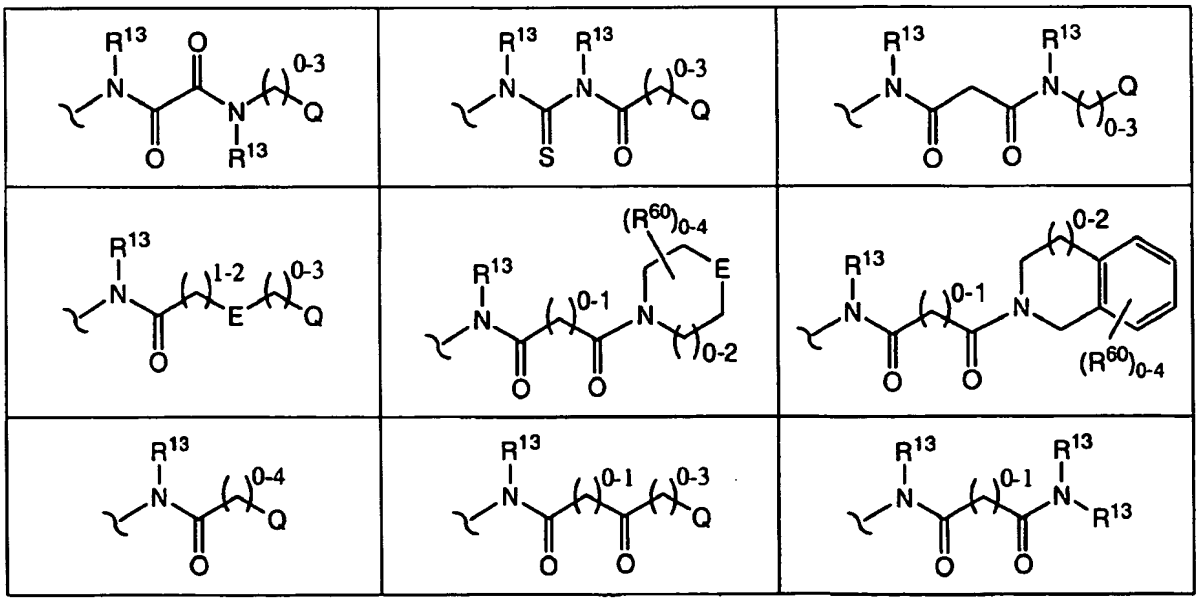
[0019] In another example, the process is according to paragraph [0018], wherein D is -O-.

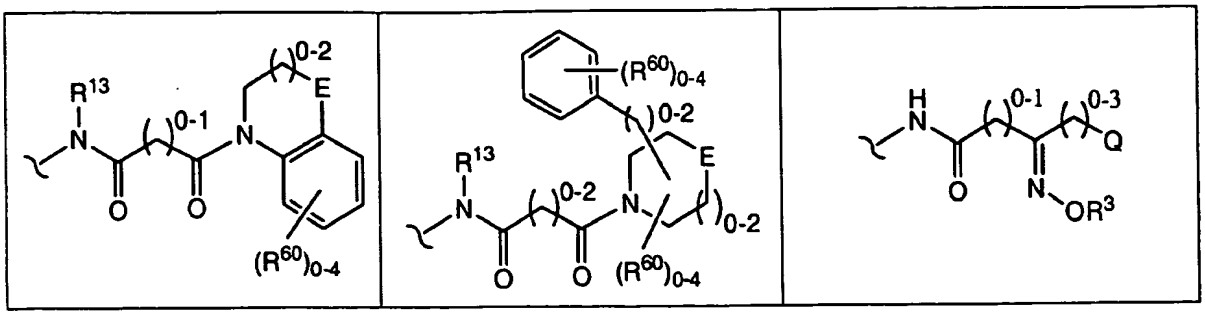
[0020] In another example, the process is according to paragraph [0019], wherein $-O-R^{50}$ and $-OR^{3a}$ are interchangeably located at the 6-position and 7-position of the quinazoline or quinoline according to Formula **I**.

[0021] In another example, the process is according to paragraph [0020], wherein $-OR^{3a}$ is -OH or optionally substituted $-OC_{1-6}$alkyl.

[0022] In another example, the process is according to paragraph [0021], wherein J is =N- or =C(H)-.

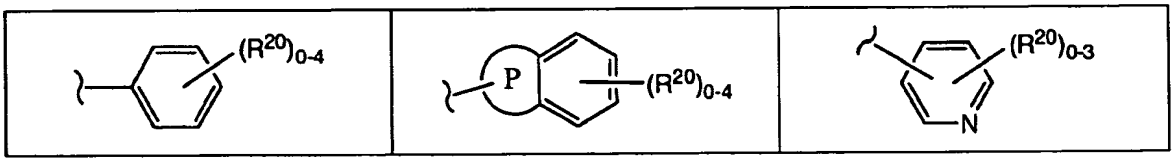
[0023] In another example, the process is according to paragraph [0022], wherein -B-L-T is selected from:





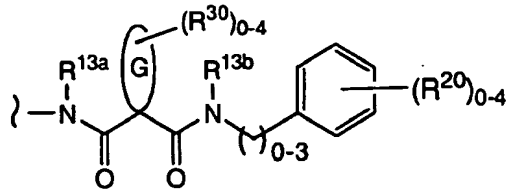
wherein Q, R^{20}, R^{13}, E, and R^{60} are as defined above; each methylene in any of the above formulae, other than those in a depicted ring, is independently optionally substituted with R^{25}; and R^{25} is selected from halogen, trihalomethyl, oxo, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, heteroaryl C_{1-6}alkyl, and optionally substituted C_{1-6}alkyl; two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered optionally substituted alicyclic or heteroalicyclic.

[0024] In another example, the process is according to paragraph [0023], wherein Q is selected from the following three formula:

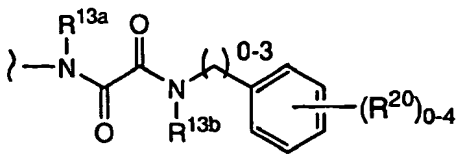


wherein R^{20} is defined as above, and P is a five- to seven-membered ring, including the two shared carbons of the aromatic ring to which P is fused, P optionally containing between one and three heteroatoms.

[0025] . In another example, the process is according to paragraph [0024], wherein -B-L-T is either of formula **V** or formula **VI**,



V

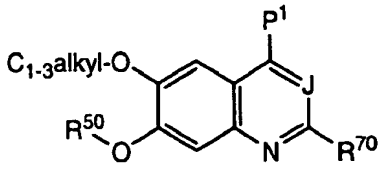


VI

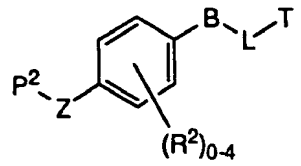
wherein R^{20} is defined as above; G is either an optionally substituted cycloalkyl or an optionally substituted heteroalicyclic; each R^{30} is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$,

$-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted C_{1-6}alkyl; and R^{3a} and R^{3b} are each independently selected from -H and optionally substituted C_{1-6}alkyl.

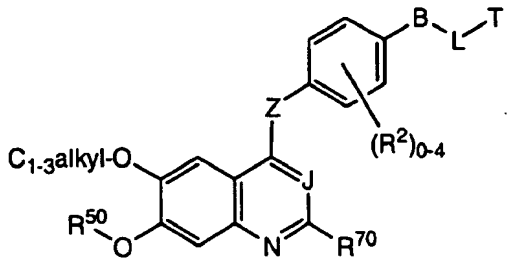
[0026] In another example, the process is according to paragraph [0025], wherein a compound of formula **IIa** is combined with a compound of formula **IIIa** to make a compound of formula **Ia**,



IIa



IIIa



Ia

wherein -B-L-T, Z, J, R^{50}, and R^2 are as defined above; R^{70} is selected from -H, $-NO_2$, $-NH_2$, and $-NR^3R^3$; provided when Z is $-N(R^5)-$ that R^5 is selected from -H, C_{1-3}alkyl, and aryl C_{1-3}alkyl; P^1 is selected from halogen, optionally substituted alkyl-$S(O)_{0-2}$-, optionally substituted arylsulfonate, optionally substituted alkylsulfonate, a group containing boron, an azide, a group containing phosphorus, and a metal; and P^2 is selected from -H and a metal.

[0027] In another example, the process is according to paragraph [0026], wherein P^2 is selected from -H, lithium, sodium, potassium, cesium, copper, palladium, and titanium.

[0028] In another example, the process is according to paragraph [0027], wherein Z is -O-.

[0029] In another example, the process is according to paragraph [0028], wherein P^1 is selected from chlorine, bromine, a toluene sulfonate, and trifluoromethansulfonate.

[0030] In another example, the process is according to paragraph [0029], wherein R^{70} is -H.

[0031] In another example, the process is according to paragraph [0030], wherein J is =C(H)-.

[0032] In another example, the process is according to paragraph [0031], wherein R^2 is fluorine and there are up to three of R^2.

[0033] In another example, the process is according to paragraph [0032], wherein **IIa** and **IIIa** are heated together, optionally with a base, optionally with microwave radiation, to form **Ia**.

[0034] In another example, the process is according to paragraph [0033], wherein the base is selected from an organic base, an inorganic base, and a combination of an organic base and an inorganic base.

[0035] In another example, the process is according to paragraph [0034], wherein the base is selected from 2,6-lutidine, 4-N,N-dimethylaminopyridine, and a metal carbonate.

[0036] In another example, the process is according to paragraph [0035], wherein **IIa** and **IIIa** are heated together in a solvent with said base, at between about 40°C and 200°C for between about one hour and twenty-four hours to form **Ia**.

[0037] In another example, the process is according to paragraph [0036], wherein the solvent is an organic solvent.

[0038] In another example, the process is according to paragraph [0037], wherein one molar equivalent of **IIa** is combined with between about one quarter and four molar equivalents of **IIIa**.

[0039] In another example, the process is according to paragraph [0038], wherein one molar equivalent of **IIa** is combined with more than one but less than two molar equivalents of **IIIa**.

[0040] In another example, the process is according to paragraph [0039], wherein **IIa** is combined with **IIIa** and said base in an aromatic solvent to form a mixture, and said mixture is heated to between about 100°C and 200°C for between about one and ten hours to form **Ia**.

[0041] In another example, the process is according to paragraph [0040], wherein the aromatic solvent is an optionally substituted benzene.

[0042] In another example, the process is according to paragraph [0041], wherein the aromatic solvent is bromobenzene.

[0043] In another example, the process is according to paragraph [0042], wherein the base is 4-N,N-dimethylaminopyridine.

[0044] In another example, the process is according to paragraph [0043], wherein said mixture is heated to reflux for between about three and seven hours.

[0045] In another example, the process is according to paragraph [0044], wherein said mixture is heated to reflux for between about four and six hours.

[0046] In another example, the process is according to paragraph [0039], wherein **IIa** is combined with **IIIa** and said base in a non-aromatic solvent to form a mixture, and said mixture is heated to between about 40°C and 100°C for between about one and twenty hours to form **Ia**.

[0047] In another example, the process is according to paragraph [0046], wherein the non-aromatic solvent comprises a functional group selected from an amide, and ether, a nitrile, a halide, an ester, an amine, and a ketone.

[0048] In another example, the process is according to paragraph [0047], wherein the non-aromatic solvent is N,N-dimethylacetamide.

[0049] In another example, the process is according to paragraph [0048], wherein the base is potassium carbonate.

[0050] In another example, the process is according to paragraph [0049], wherein said mixture is heated to about 50°C between about ten and twenty hours.

[0051] In another example, the process is according to paragraph [0040], wherein the aromatic solvent is an optionally substituted pyridine.

[0052] In another example, the process is according to paragraph [0051], wherein the aromatic solvent is 2,6-lutidine.

[0053] In another example, the process is according to paragraph [0052], wherein the base is 2,6-lutidine.

[0054] In another example, the process is according to paragraph [0053], wherein said mixture is heated to reflux for between about three and seven hours.

[0055] In another example, the process is according to paragraph [0054], wherein said mixture is heated to reflux for between about four and six hours.

[0056] In another example, the process is according to paragraph [0038], wherein one molar equivalent of **IIIa** is combined with more than one but less than two molar equivalents of **IIa**.

[0057] In another example, the process is according to paragraph [0056], wherein **IIa** is combined with **IIIa** and said base in an aromatic solvent to form a mixture, and said mixture is heated to between about 100°C and 200°C for between about ten and twenty hours to form **Ia**.

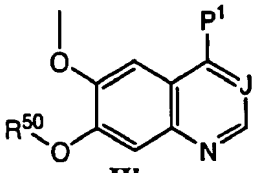
[0058] In another example, the process is according to paragraph [0057], wherein the aromatic solvent is an optionally substituted pyridine.

[0059] In another example, the process is according to paragraph [0058], wherein the aromatic solvent is 2,6-lutidine.

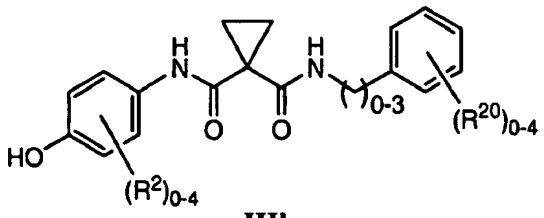
[0060] In another example, the process is according to paragraph [0059], wherein the base is 2,6-lutidine.

[0061] In another example, the process is according to paragraph [0060], wherein said mixture is heated to between about 150°C and 200°C for between about fifteen and twenty hours.

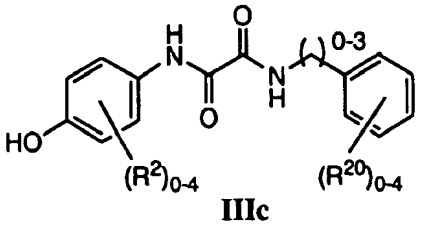
[0062] In another example, the process is according to any of paragraphs [0033] – [0061], wherein a compound of formula **IIb** is substituted for the compound of formula **IIa**, and either a compound of formula **IIIb** or a compound of formula **IIIc** is substituted for the compound of formula **IIIa**, in order to make a compound of formula **Ib** or a compound of formula **Ic**, respectively,



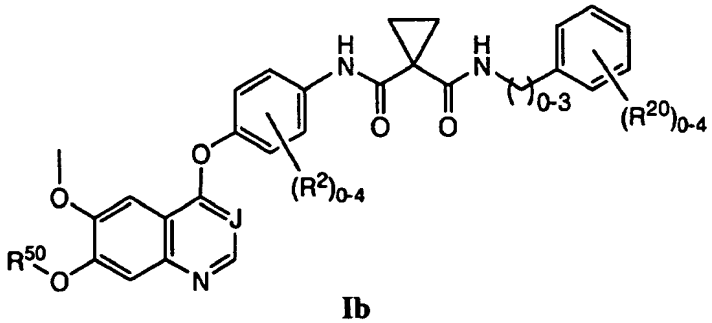
IIb



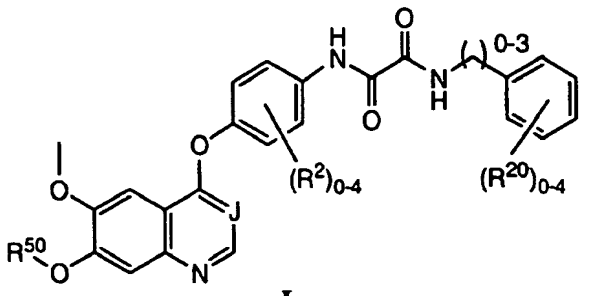
IIIb



IIIc



Ib



Ic

wherein J, R^{50}, R^{20} and R^2 are as defined above.

[0063] In another example, the process is according to paragraph [0062], wherein R^2, if present, is fluorine.

[0064] In another example, the process is according to paragraph [0063], wherein R^2, if present, is up to two fluorines *ortho* to the oxygen of the phenylene.

[0065] In another example, the process is according to paragraph [0014], used to make a compound listed in Table 1.

Table 1

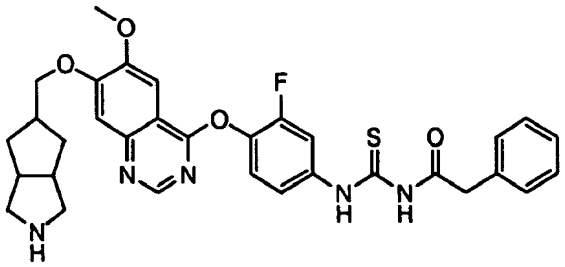
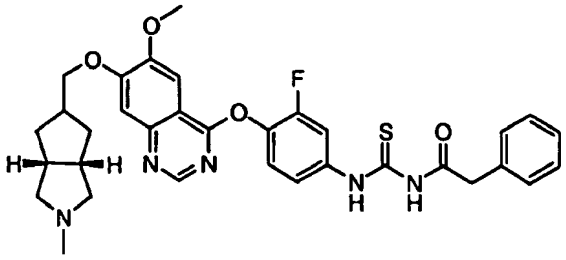
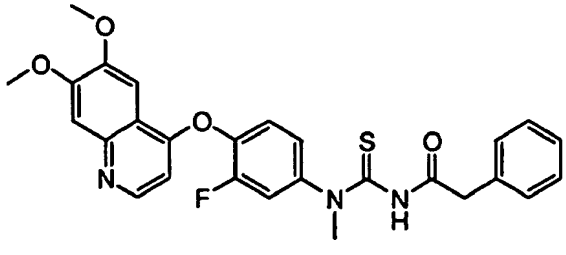
Entry	Name	Structure
1	N-[({3-fluoro-4-[(6-(methyloxy)-7-{[(3aR,6aS)-octahydrocyclopenta[c]pyrrol-5-ylmethyl]oxy}quinazolin-4-yl)oxy]phenyl}amino)carbonothioyl]-2-phenylacetamide	
2	N-{[(3-fluoro-4-{[7-({[(3aR,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-yl]oxy}phenyl)amino]carbonothioyl}-2-phenylacetamide	
3	N-{[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)(methyl)amino]carbonothioyl}-2-phenylacetamide	

Table 1

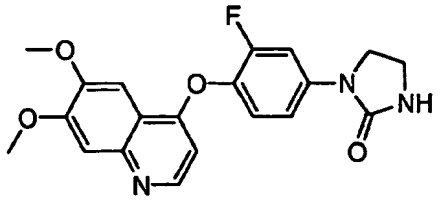
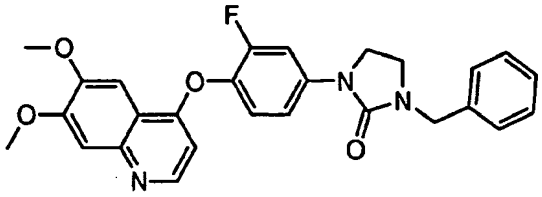
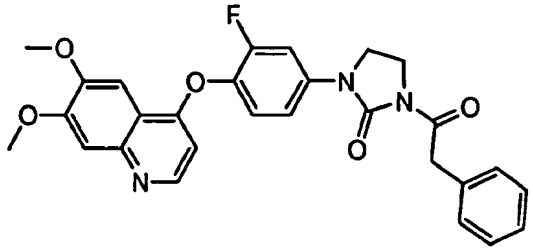
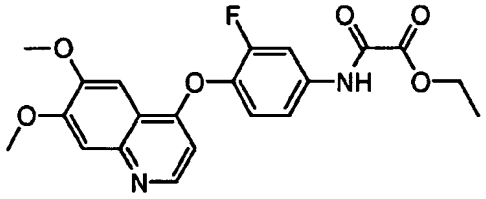
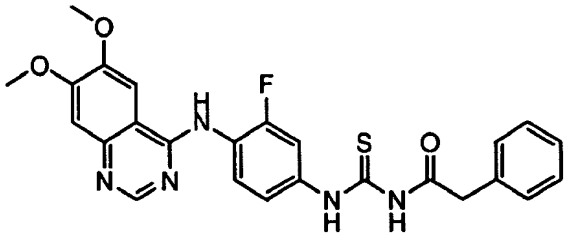
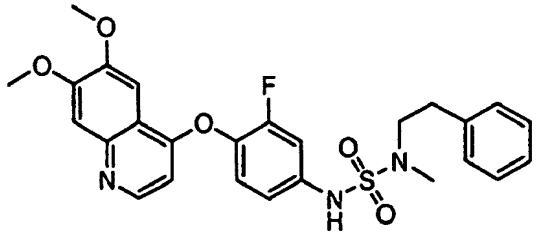
Entry	Name	Structure
4	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)imidazolidin-2-one	
5	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylmethyl)imidazolidin-2-one	
6	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylacetyl)imidazolidin-2-one	
7	ethyl [(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino](oxo)acetate	
8	N-{[(4-{[6,7-bis(methyloxy)quinazolin-4-yl]amino}-3-fluorophenyl)amino]carbonothioyl}-2-phenylacetamide	
9	N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-methyl-N-(2-phenylethyl)sulfamide	

Table 1

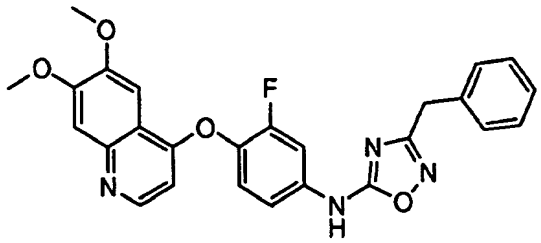
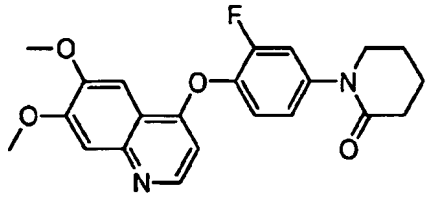
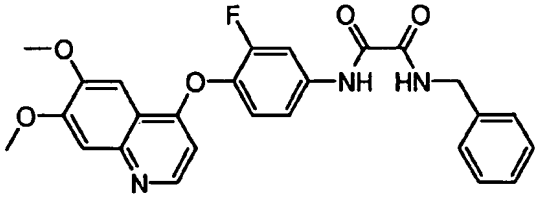
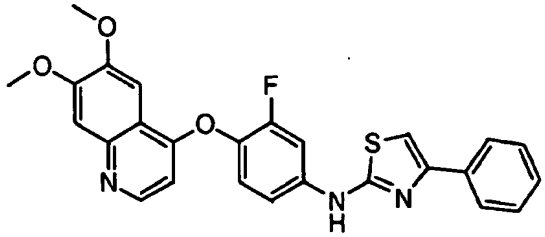
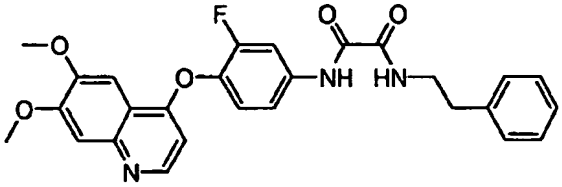
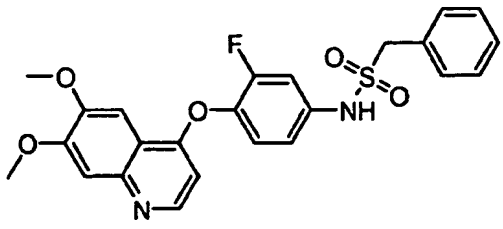
Entry	Name	Structure
10	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylmethyl)-1,2,4-oxadiazol-5-amine	
11	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)piperidin-2-one	
12	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(phenylmethyl)ethanediamide	
13	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-4-phenyl-1,3-thiazol-2-amine	
14	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylethyl)ethanediamide	
15	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-1-phenylmethanesulfonamide	

Table 1

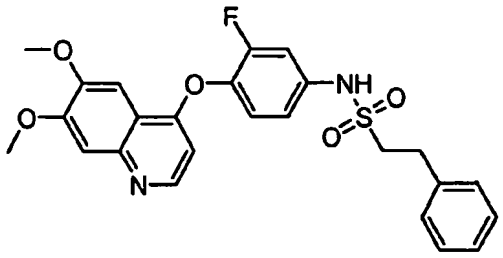
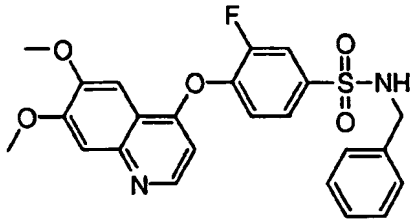
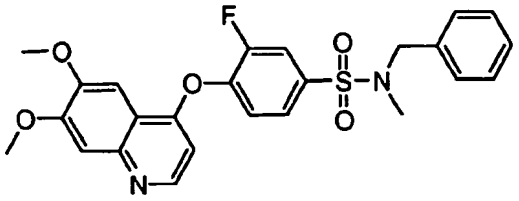
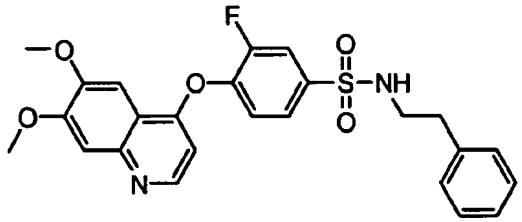
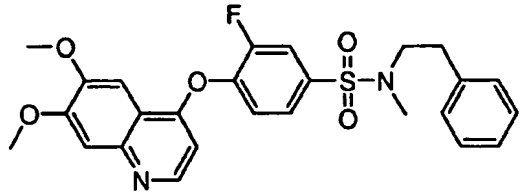
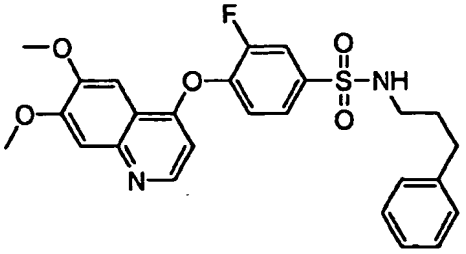
Entry	Name	Structure
16	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-2-phenylethanesulfonamide	
17	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(phenylmethyl)benzenesulfonamide	
18	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(phenylmethyl)benzenesulfonamide	
19	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(2-phenylethyl)benzenesulfonamide	
20	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(2-phenylethyl)benzenesulfonamide	
21	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(3-phenylpropyl)benzenesulfonamide	

Table 1

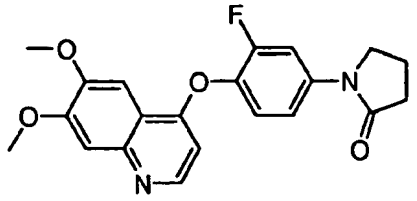
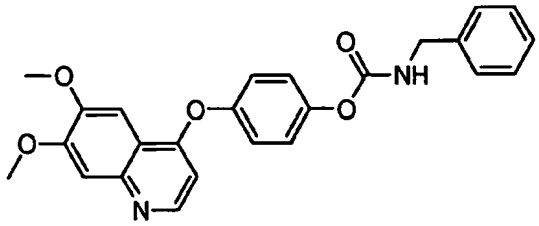
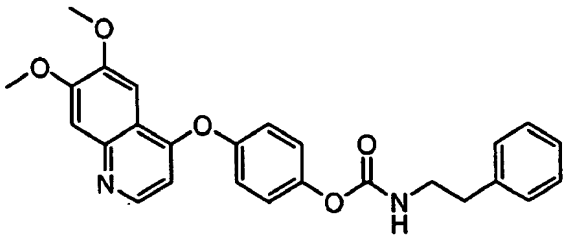
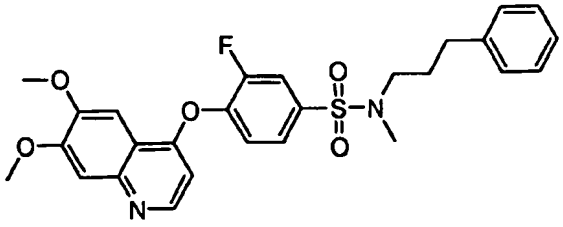
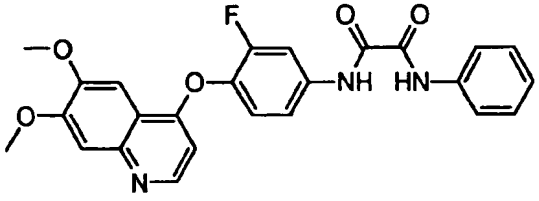
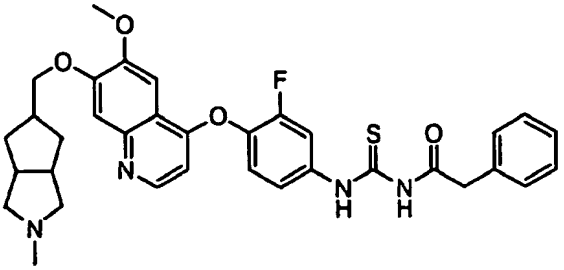
Entry	Name	Structure
22	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)pyrrolidin-2-one	
23	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (phenylmethyl)carbamate	
24	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (2-phenylethyl)carbamate	
25	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(3-phenylpropyl)benzenesulfonamide	
26	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-phenylethanediamide	
27	N-{[(3-fluoro-4-{[7-{[(2-methyloctahydrocyclopenta[c]pyrrol-5-yl)methyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}phenyl)amino]carbonothioyl}-2-phenylacetamide	

Table 1

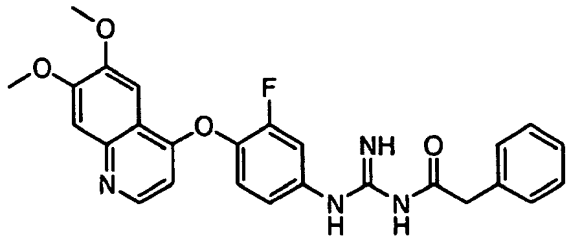
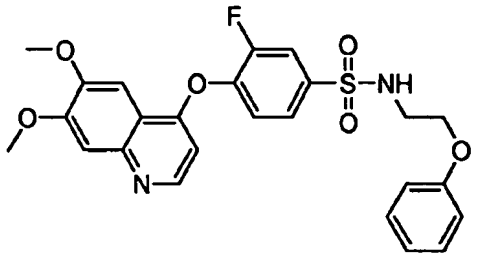
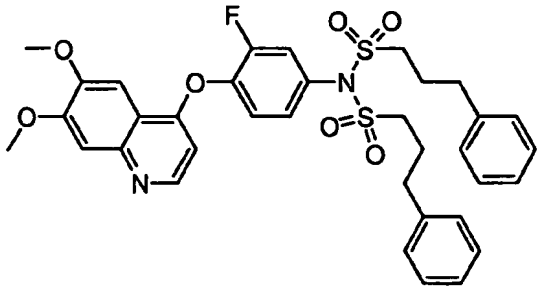
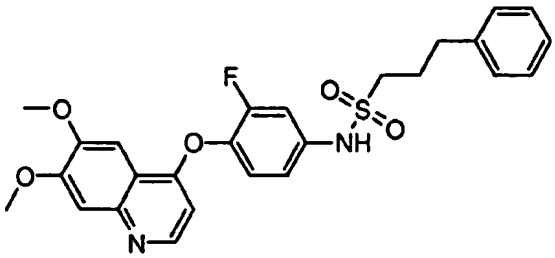
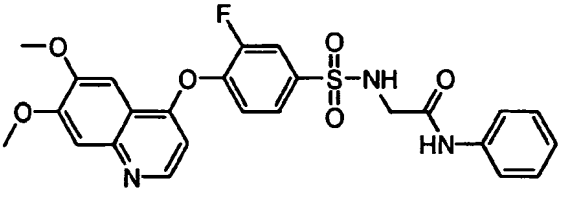
Entry	Name	Structure
28	N-[(Z)-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino](imino)methyl]-2-phenylacetamide	
29	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-[2-(phenyloxy)ethyl]benzenesulfonamide	
30	N,N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-bis-(3-phenylpropane-1-sulfonamide)	
31	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-phenylpropane-1-sulfonamide	
32	N2-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)sulfonyl]-N1-phenylglycinamide	

Table 1

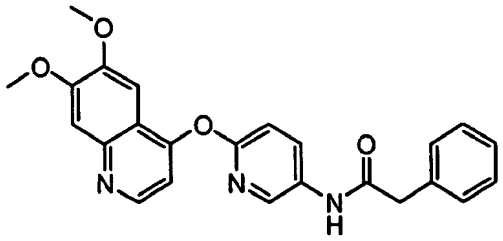
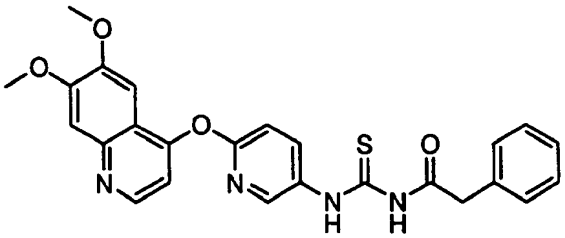
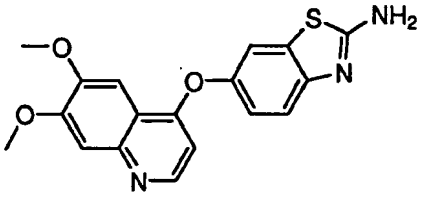
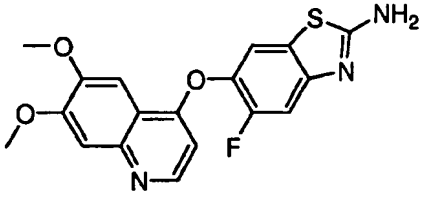
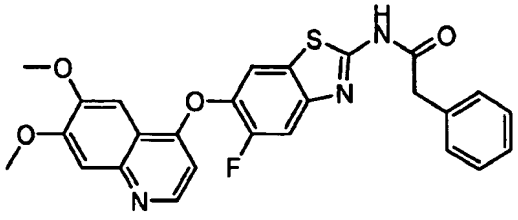
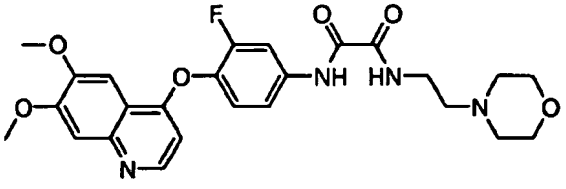
Entry	Name	Structure
33	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-2-phenylacetamide	
34	N-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide	
35	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-amine	
36	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-amine	
37	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-phenylacetamide	
38	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-morpholin-4-ylethyl)ethanediamide	

Table 1

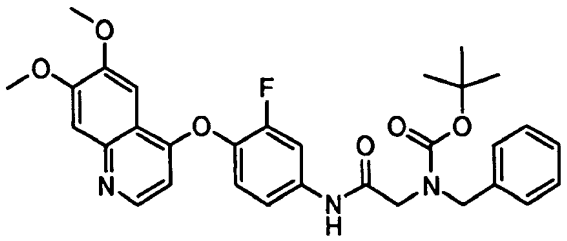
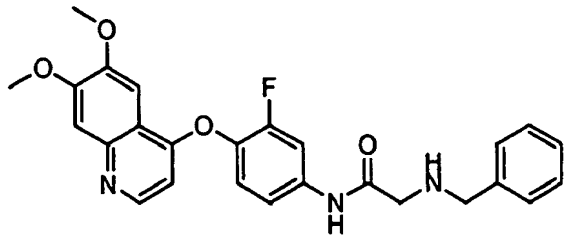
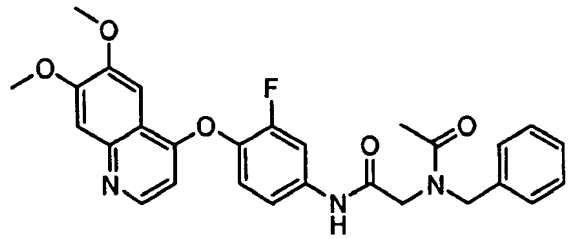
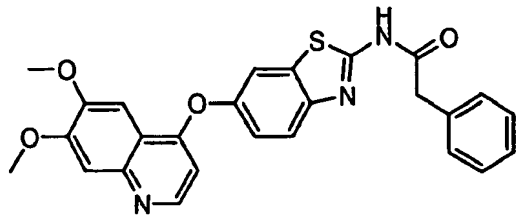
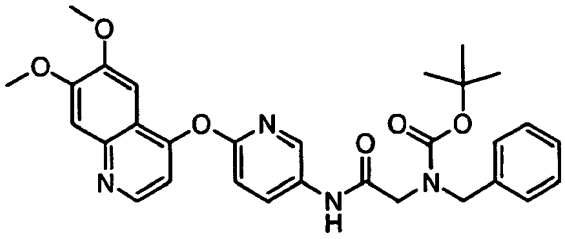
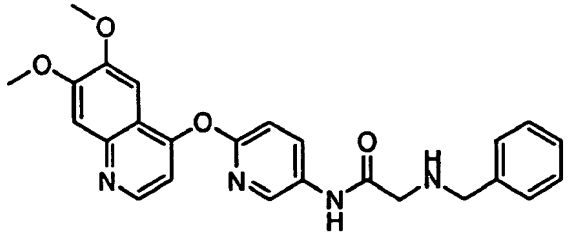
Entry	Name	Structure
39	benzyl-{[4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylcarbamoyl]-methyl}-carbamic acid tert-butyl ester	
40	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(phenylmethyl)glycinamide	
41	N2-acetyl-N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(phenylmethyl)glycinamide	
42	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-yl)-2-phenylacetamide	
43	benzyl-{[6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-ylcarbamoyl]-methyl}-carbamic acid tert-butyl ester	
44	N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-(phenylmethyl)glycinamide	

Table 1

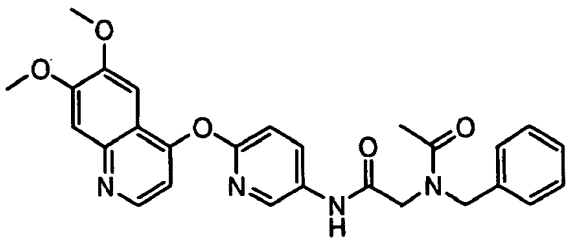
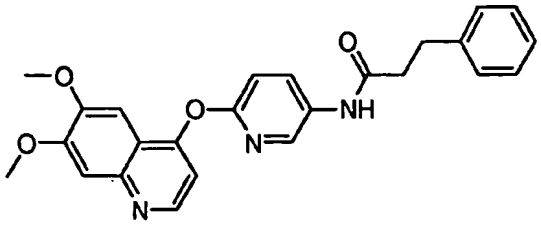
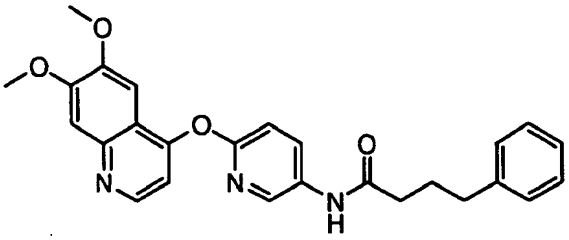
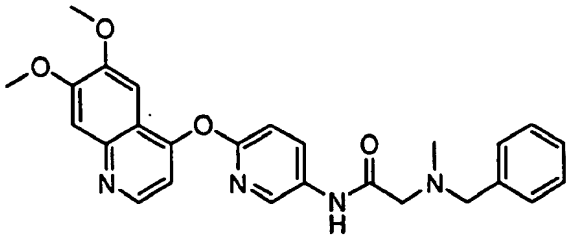
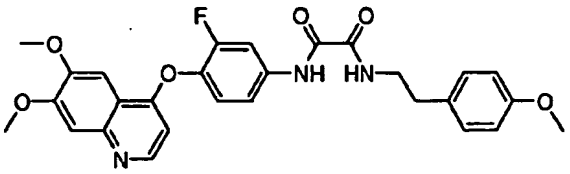
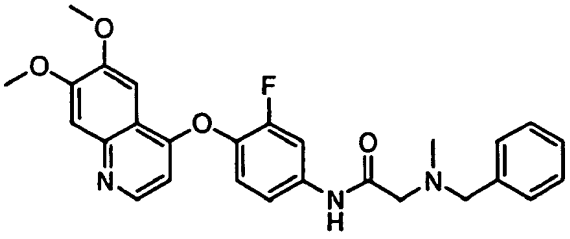
Entry	Name	Structure
45	N2-acetyl-N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-(phenylmethyl)glycinamide	
46	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-3-phenylpropanamide	
47	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-4-phenylbutanamide	
48	N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-methyl-N2-(phenylmethyl)glycinamide	
49	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{2-[4-(methyloxy)phenyl]ethyl}ethanediamide	
50	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-(phenylmethyl)glycinamide	

Table 1

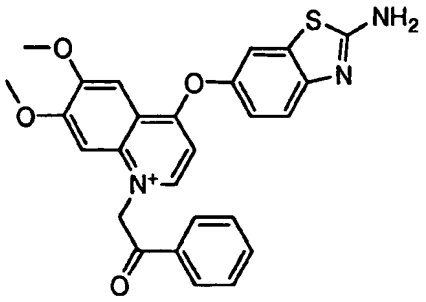
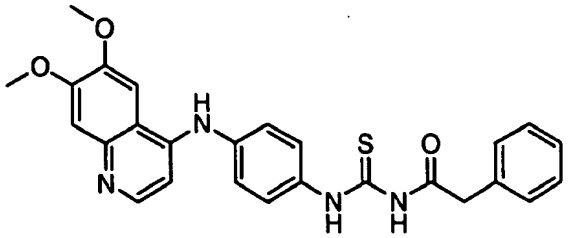
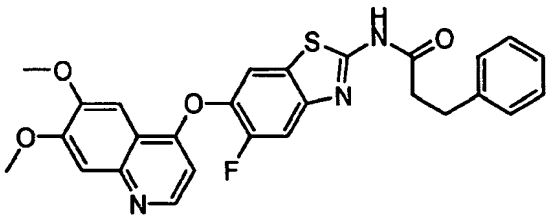
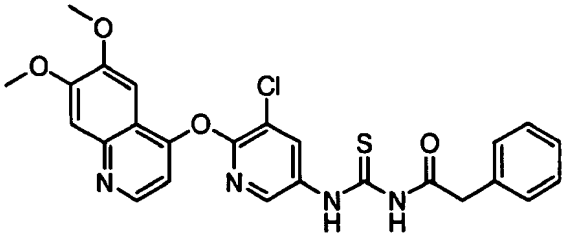
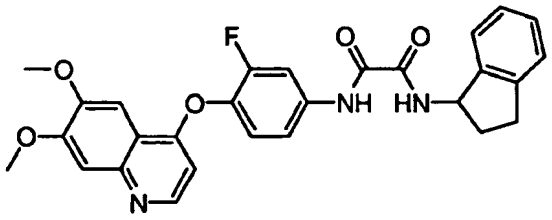
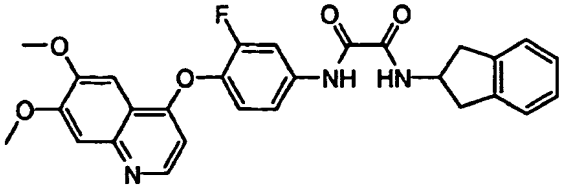
Entry	Name	Structure
51	4-[(2-amino-1,3-benzothiazol-6-yl)oxy]-6,7-bis(methyloxy)-1-(2-oxo-2-phenylethyl)quinolinium	
52	N-{[(4-{[6,7-bis(methyloxy)quinolin-4-yl]amino}phenyl)amino]carbonothioyl}-2-phenylacetamide	
53	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-3-phenylpropanamide	
54	N-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide	
55	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2,3-dihydro-1H-inden-1-yl)ethanediamide	
56	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2,3-dihydro-1H-inden-2-yl)ethanediamide	

Table 1

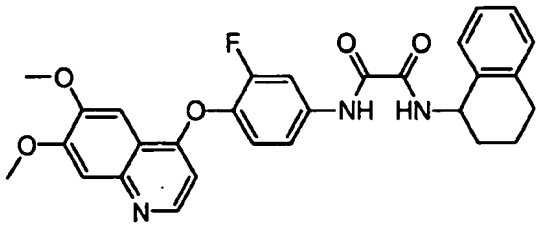
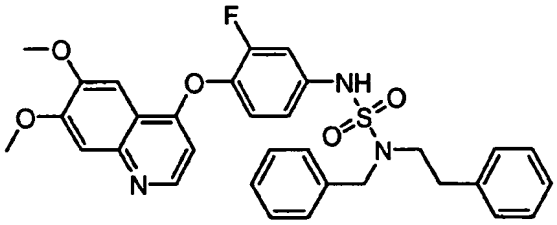
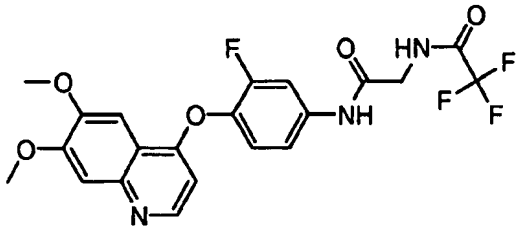
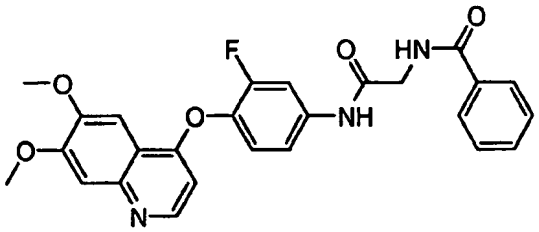
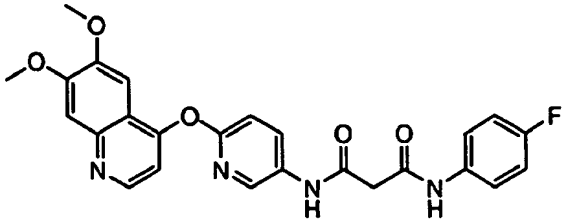
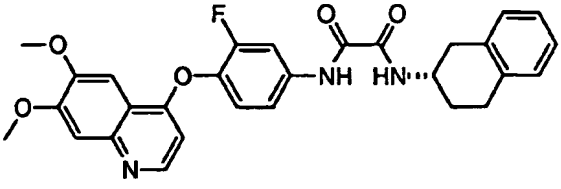
Entry	Name	Structure
57	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydronaphthalen-1-yl)ethanediamide	
58	N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-(2-phenylethyl)-N-(phenylmethyl)sulfamide	
59	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(trifluoroacetyl)glycinamide	
60	N-{[4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylcarbamoyl]-methyl}-benzamide	
61	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N'-(4-fluorophenyl)propanediamide	
62	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2S)-1,2,3,4-tetrahydronaphthalen-2-yl]ethanediamide	

Table 1

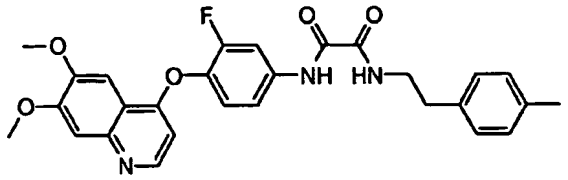
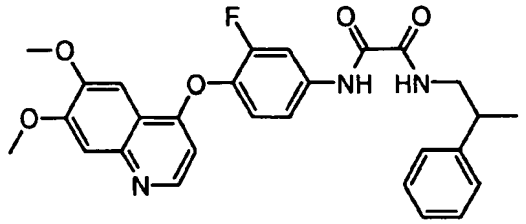
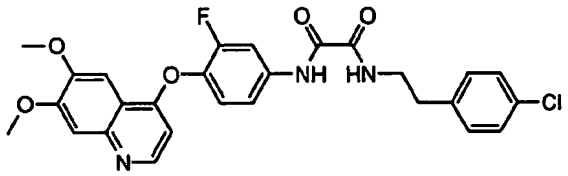
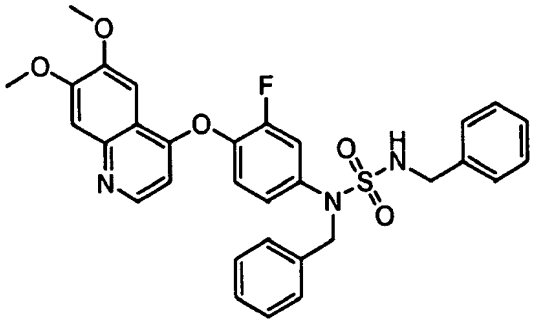
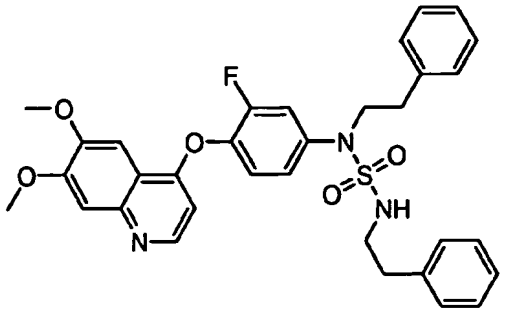
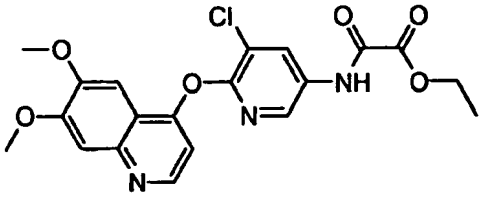
Entry	Name	Structure
63	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(4-methylphenyl)ethyl]ethanediamide	
64	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylpropyl)ethanediamide	
65	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(4-chlorophenyl)ethyl]ethanediamide	
66	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N,N'-bis(phenylmethyl)sulfamide	
67	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N,N'-bis(2-phenylethyl)sulfamide	
68	ethyl [(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino](oxo)acetate	

Table 1

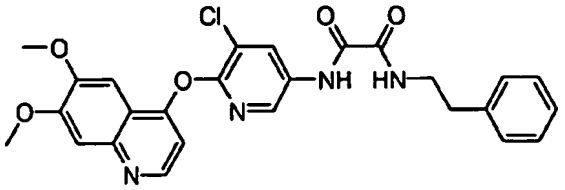
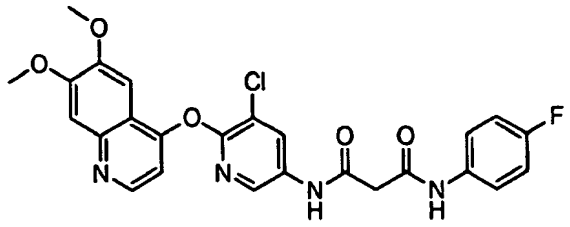
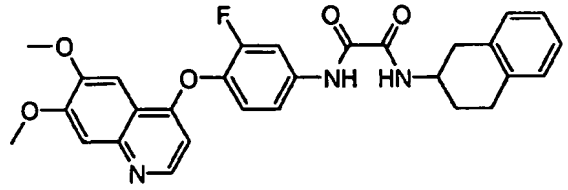
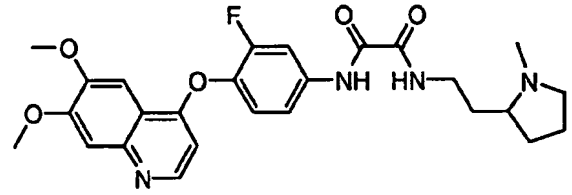
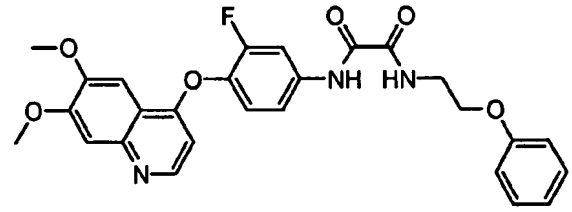
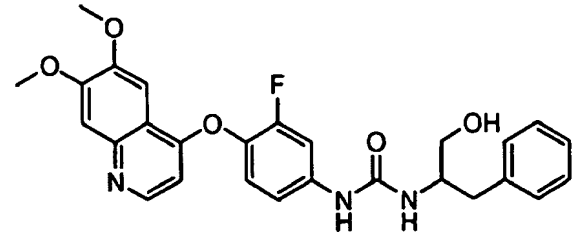
Entry	Name	Structure
69	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl)ethanediamide	
70	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)propanediamide	
71	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydronaphthalen-2-yl)ethanediamide	
72	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(1-methylpyrrolidin-2-yl)ethyl]ethanediamide	
73	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(phenyloxy)ethyl]ethanediamide	
74	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-hydroxy-1-(phenylmethyl)ethyl]urea	

Table 1

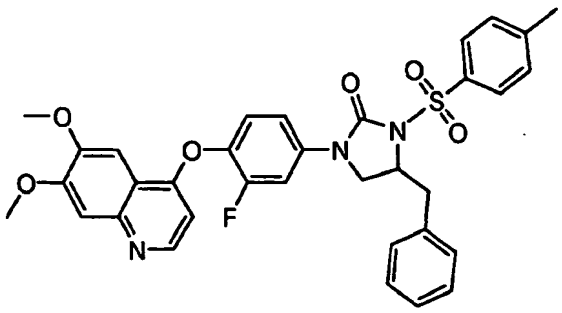
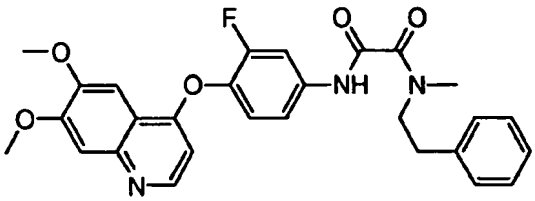
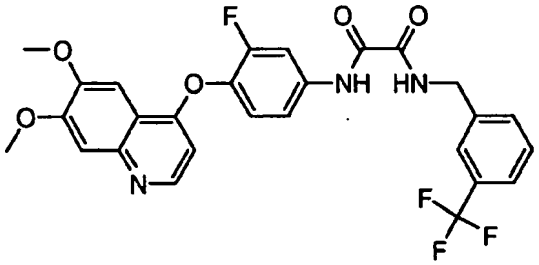
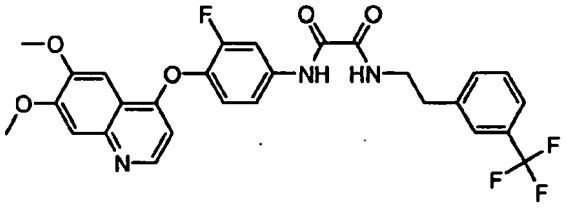
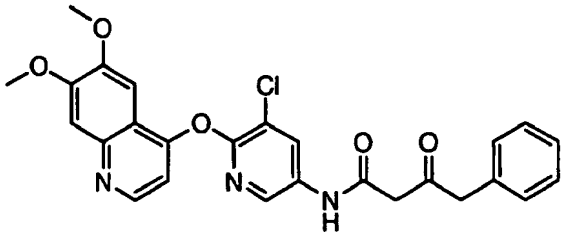
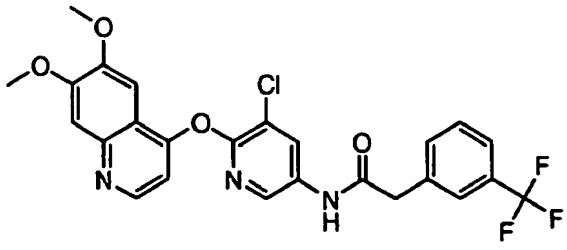
Entry	Name	Structure
75	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one	
76	N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-methyl-N-(2-phenylethyl)ethanediamide	
77	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{[3-(trifluoromethyl)phenyl]methyl}ethanediamide	
78	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{2-[3-(trifluoromethyl)phenyl]ethyl}ethanediamide	
79	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-3-oxo-4-phenylbutanamide	
80	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-2-[3-(trifluoromethyl)phenyl]acetamide	

Table 1

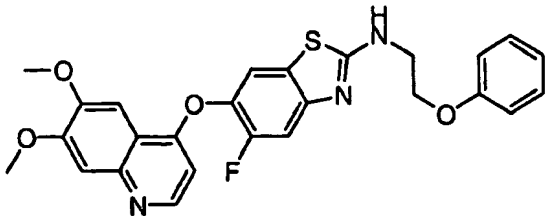
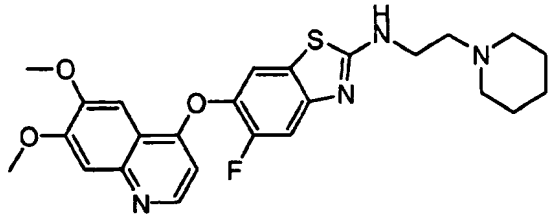
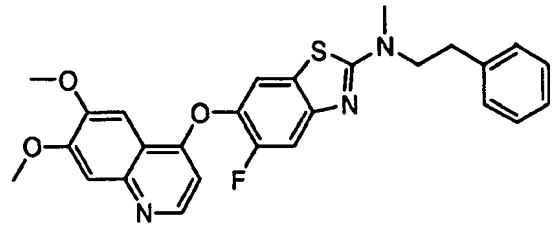
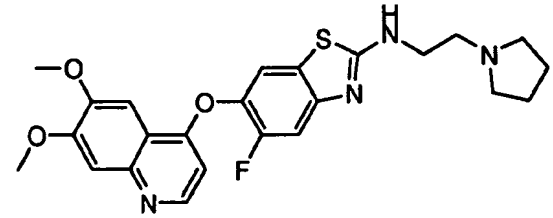
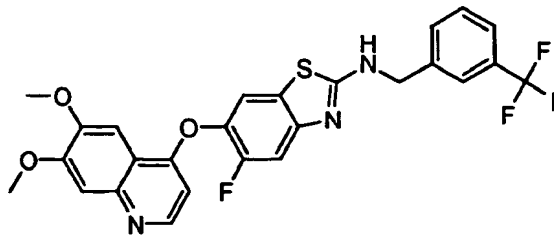
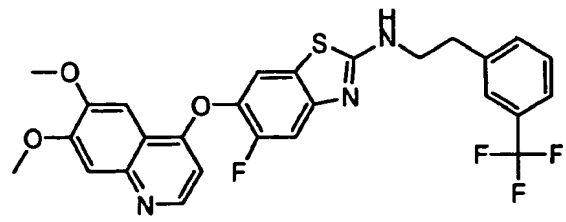
Entry	Name	Structure
81	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-[2-(phenyloxy)ethyl]-1,3-benzothiazol-2-amine	
82	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-(2-piperidin-1-ylethyl)-1,3-benzothiazol-2-amine	
83	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-methyl-N-(2-phenylethyl)-1,3-benzothiazol-2-amine	
84	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-(2-pyrrolidin-1-ylethyl)-1,3-benzothiazol-2-amine	
85	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-{[3-(trifluoromethyl)phenyl]methyl}-1,3-benzothiazol-2-amine	
86	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-{2-[3-(trifluoromethyl)phenyl]ethyl}-1,3-benzothiazol-2-amine	

Table 1

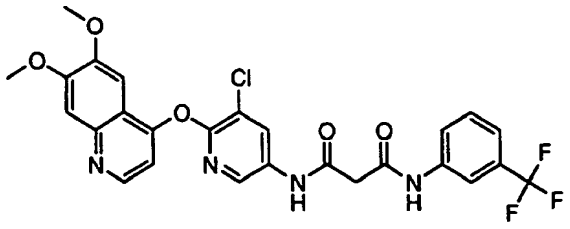
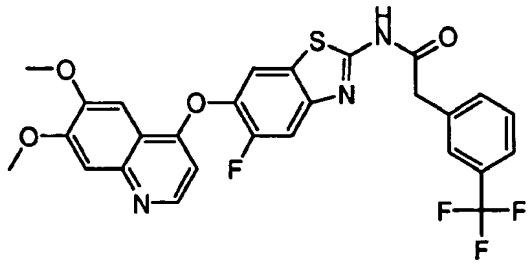
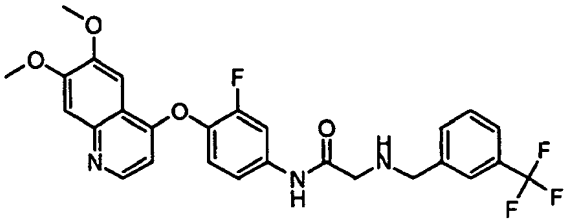
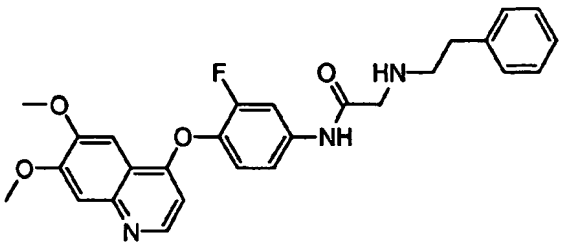
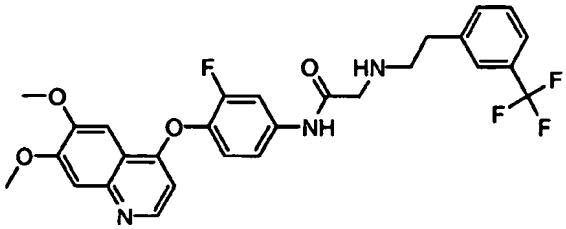
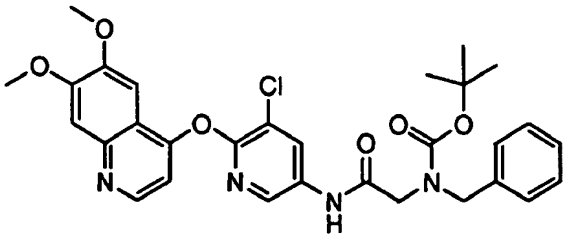
Entry	Name	Structure
87	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-[3-(trifluoromethyl)phenyl]propanediamide	
88	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3-(trifluoromethyl)phenyl]acetamide	
89	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-{[3-(trifluoromethyl)phenyl]methyl}glycinamide	
90	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(2-phenylethyl)glycinamide	
91	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-{2-[3-(trifluoromethyl)phenyl]ethyl}glycinamide	
92	benzyl-{[5-chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-ylcarbamoyl]-methyl}-carbamic acid tert-butyl ester	

Table 1

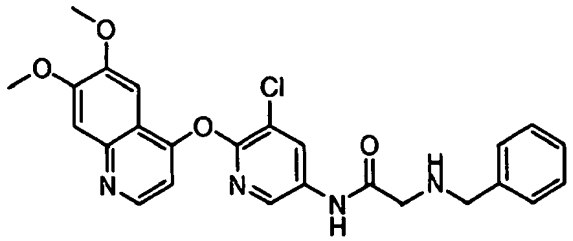
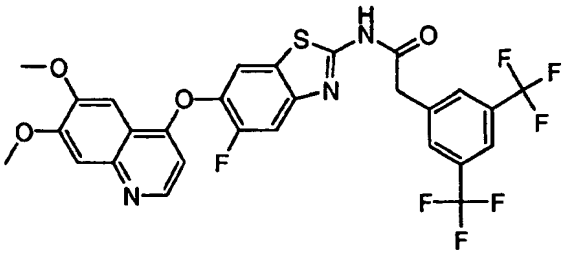
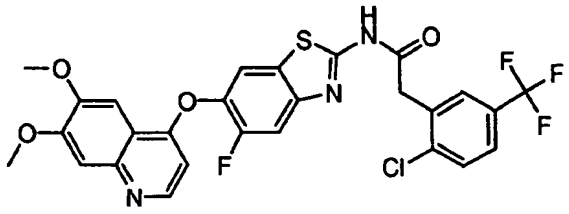
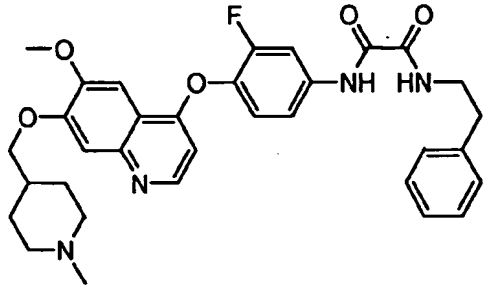
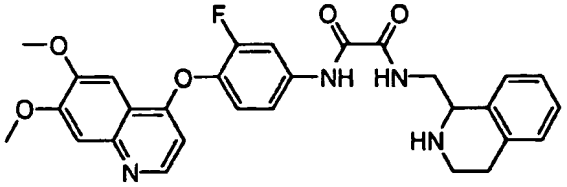
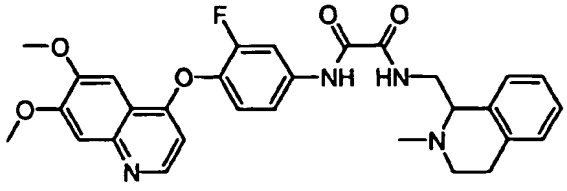
Entry	Name	Structure
93	N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N2-(phenylmethyl)glycinamide	
94	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3,5-bis(trifluoromethyl)phenyl]acetamide	
95	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[2-chloro-5-(trifluoromethyl)phenyl]acetamide	
96	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(2-phenylethyl)ethanediamide	
97	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)ethanediamide	
98	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]ethanediamide	

Table 1

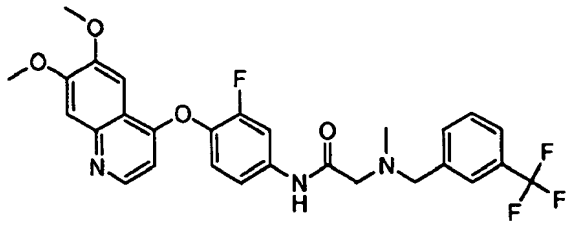
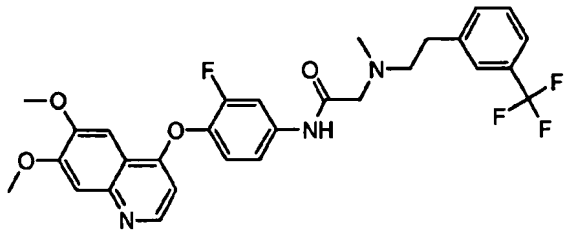
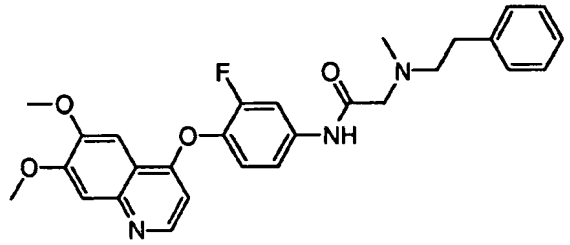
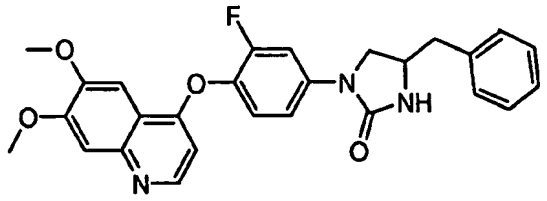
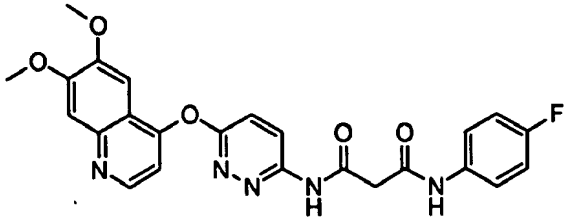
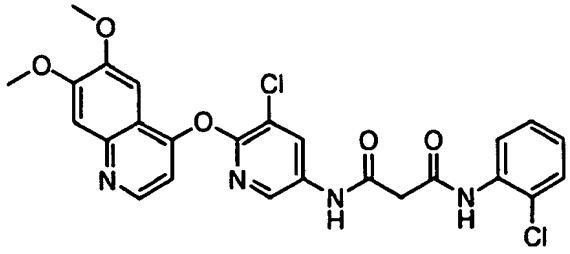
Entry	Name	Structure
99	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-{[3-(trifluoromethyl)phenyl]methyl}glycinamide	
100	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-{2-[3-(trifluoromethyl)phenyl]ethyl}glycinamide	
101	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-(2-phenylethyl)glycinamide	
102	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-4-(phenylmethyl)imidazolidin-2-one	
103	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridazin-3-yl)-N'-(4-fluorophenyl)propanediamide	
104	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-chlorophenyl)propanediamide	

Table 1

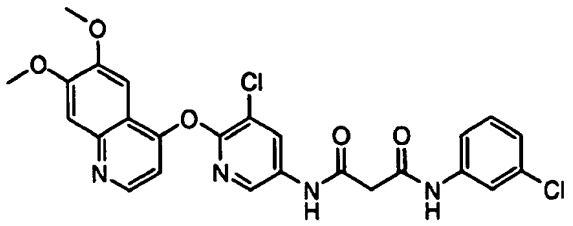
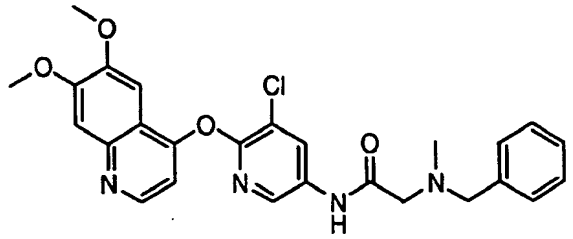
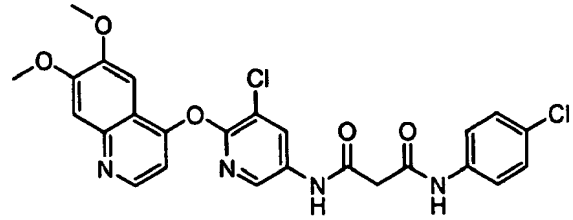
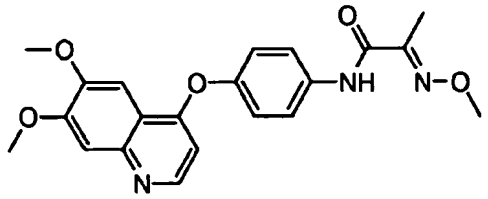
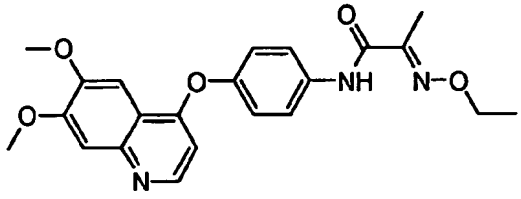
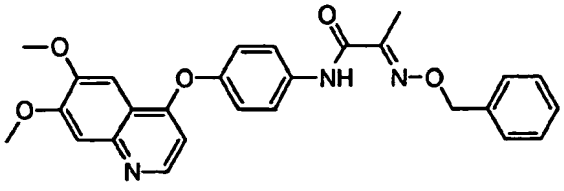
Entry	Name	Structure
105	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(3-chlorophenyl)propanediamide	
106	N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N2-methyl-N2-(phenylmethyl)glycinamide	
107	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-chlorophenyl)propanediamide	
108	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(methyloxy)imino]propanamide	
109	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(ethyloxy)imino]propanamide	
110	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-{[(phenylmethyl)oxy]imino}propanamide	

Table 1

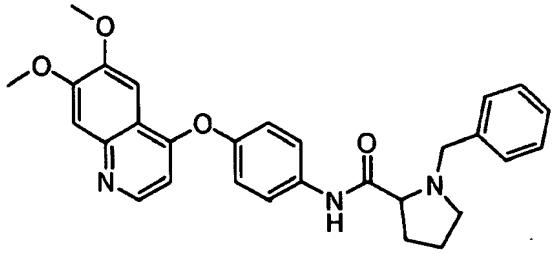
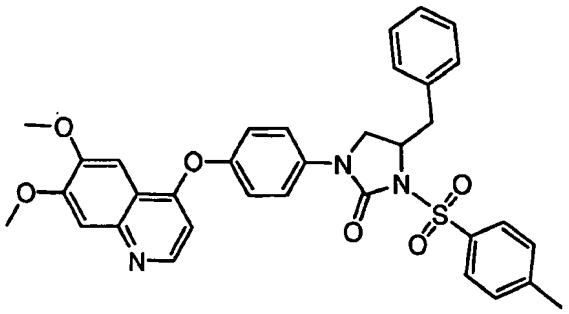
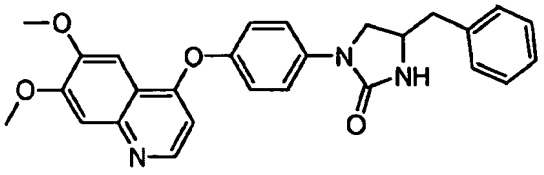
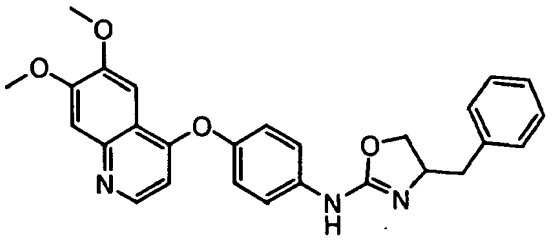
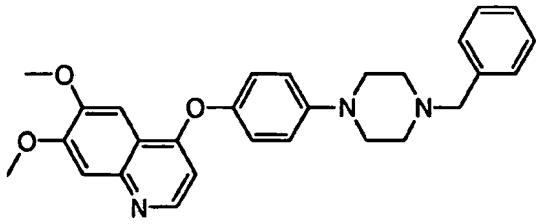
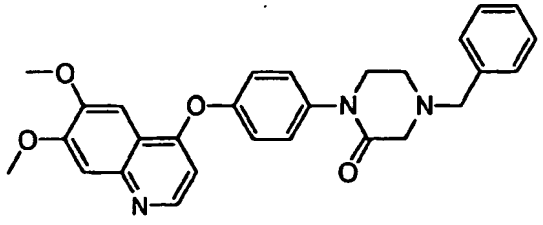
Entry	Name	Structure
111	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-1-(phenylmethyl)prolinamide	
112	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one	
113	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)imidazolidin-2-one	
114	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)-4,5-dihydro-1,3-oxazol-2-amine	
115	6,7-bis(methyloxy)-4-({4-[4-(phenylmethyl)piperazin-1-yl]phenyl}oxy)quinoline	
116	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)piperazin-2-one	

Table 1

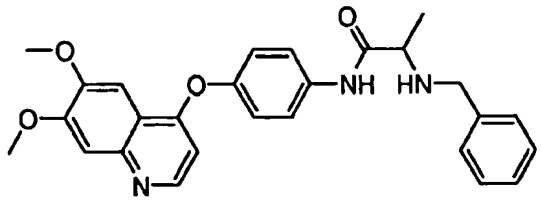
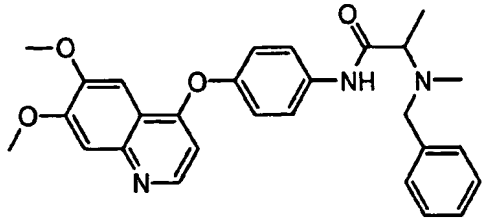
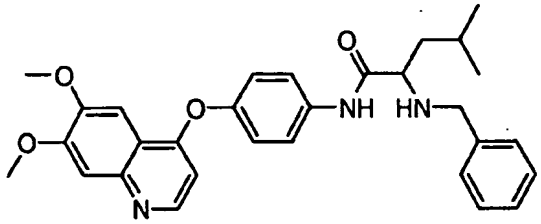
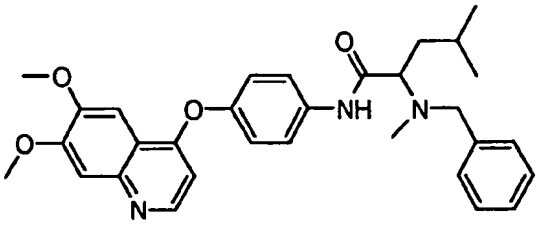
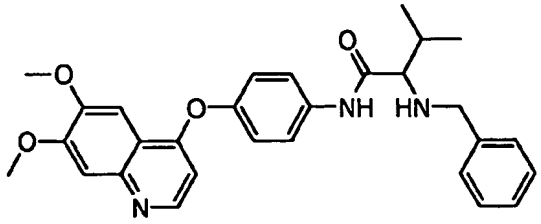
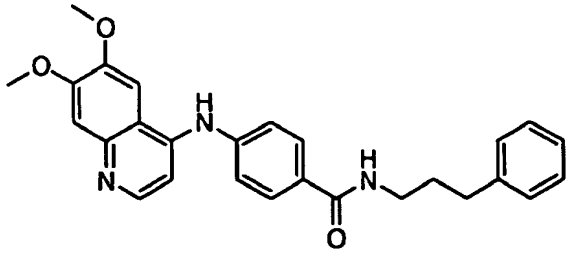
Entry	Name	Structure
117	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-(phenylmethyl)alaninamide	
118	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-methyl-N2-(phenylmethyl)alaninamide	
119	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-(phenylmethyl)leucinamide	
120	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-methyl-N2-(phenylmethyl)leucinamide	
121	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-(phenylmethyl)valinamide	
122	4-(6,7-dimethoxy-quinolin-4-ylamino)-N-(3-phenyl-propyl)-benzamide	

Table 1

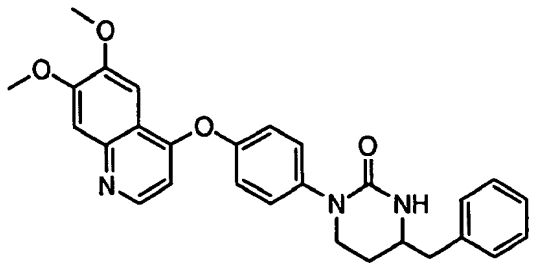
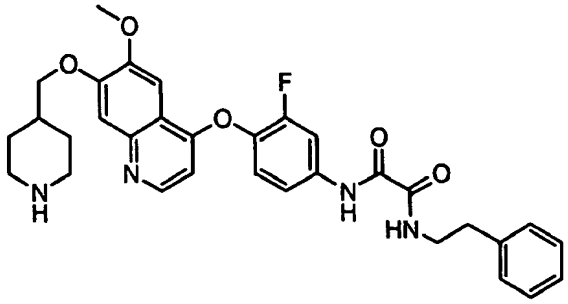
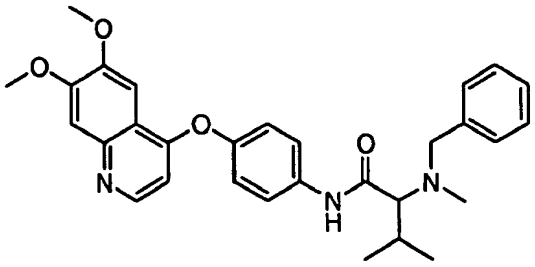
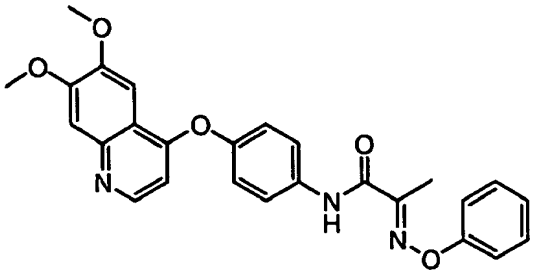
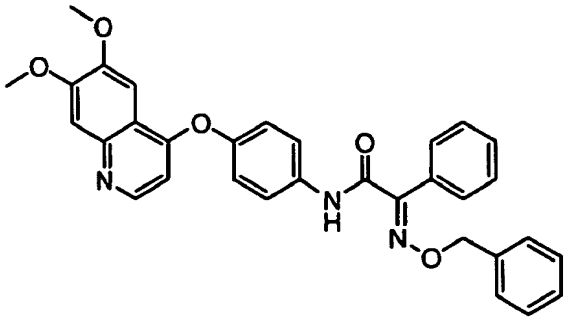
Entry	Name	Structure
123	4-benzyl-1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-tetrahydro-pyrimidin-2-one	
124	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
127	2-(Benzyl-methyl-amino)-N-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-3-methyl-butyramide (note: Alphabetic order of prefixes ignored while selecting parent chain)	
128	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenyl]-2-phenoxyimino-propionamide	
129	2-Benzyloxyimino-N-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-2-phenyl-acetamide	

Table 1

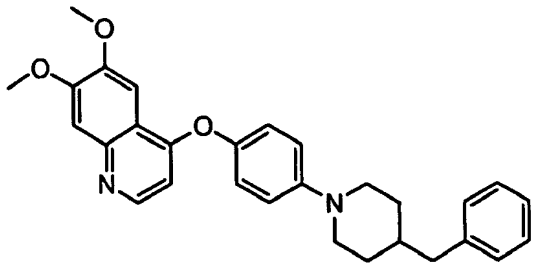
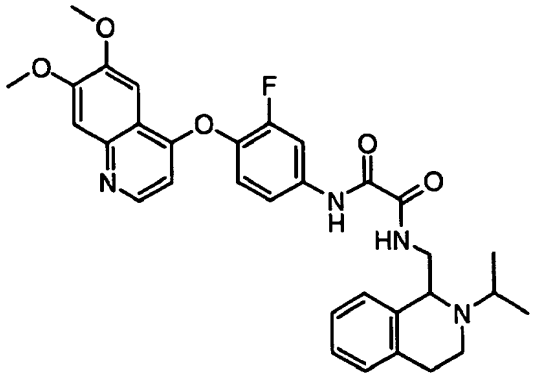
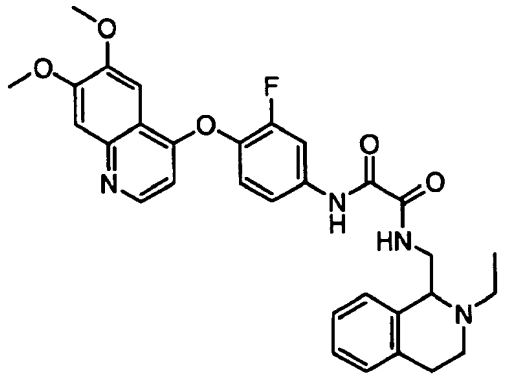
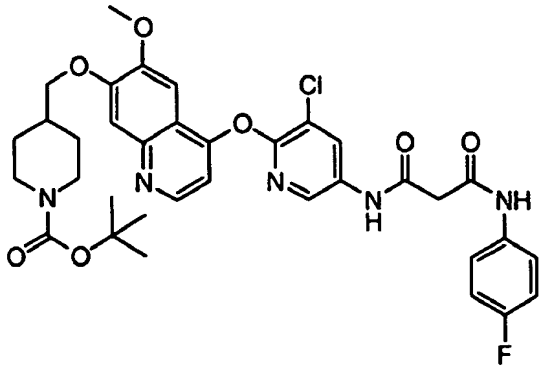
Entry	Name	Structure
130	4-[4-(4-Benzyl-piperidin-1-yl)-phenoxy]-6,7-dimethoxy-quinoline	
131	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-oxalamide	
132	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-oxalamide	
133	4-(4-{3-Chloro-5-[2-(4-fluoro-phenylcarbamoyl)-acetylamino]-pyridin-2-yloxy}-6-methoxy-quinolin-7-yloxymethyl)-piperidine-1-carboxylic acid tert-butyl ester	

Table 1

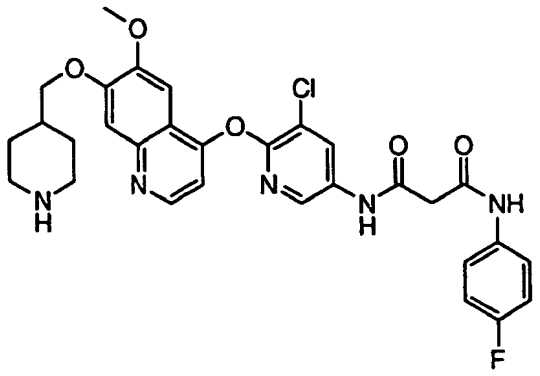
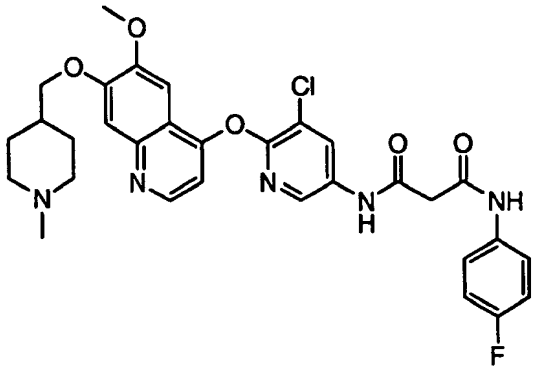
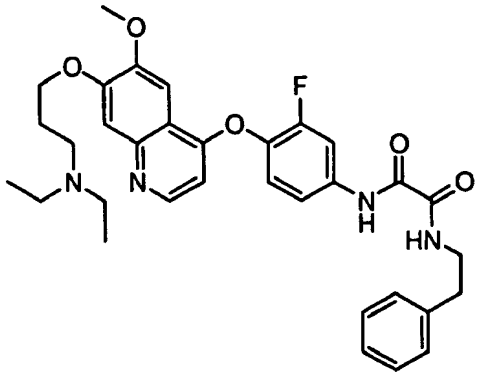
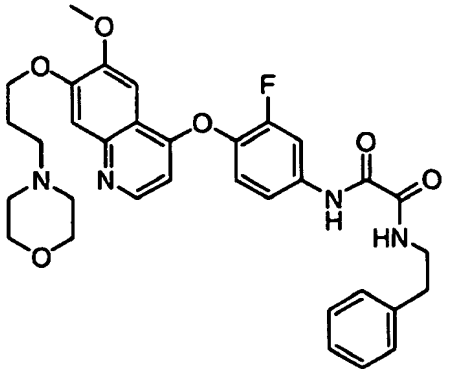
Entry	Name	Structure
134	N-{5-Chloro-6-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	
135	N-{5-Chloro-6-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	
136	N-{4-[7-(3-Diethylamino-propoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide	
137	N-{3-Fluoro-4-[6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	

Table 1

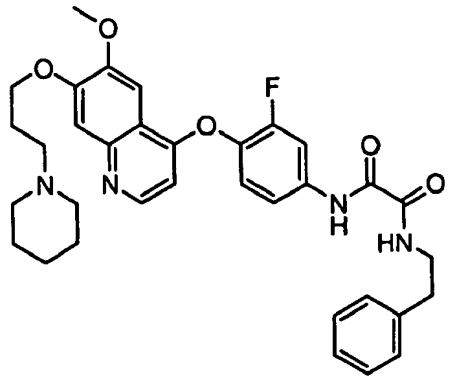
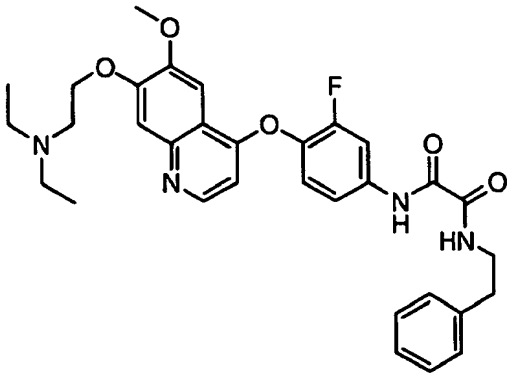
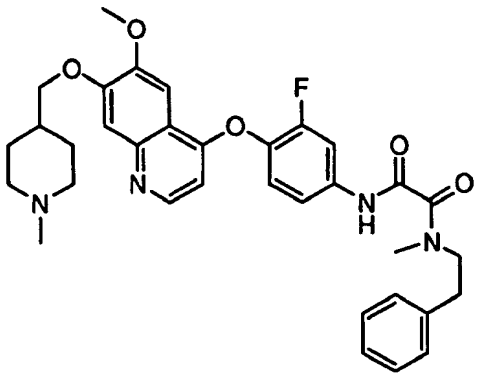
Entry	Name	Structure
138	N-{3-Fluoro-4-[6-methoxy-7-(3-piperidin-1-yl-propoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
139	N-{4-[7-(2-Diethylamino-ethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide	
140	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-methyl-N'-phenethyl-oxalamide	

Table 1

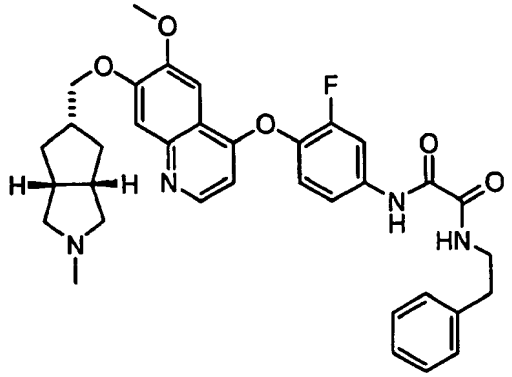
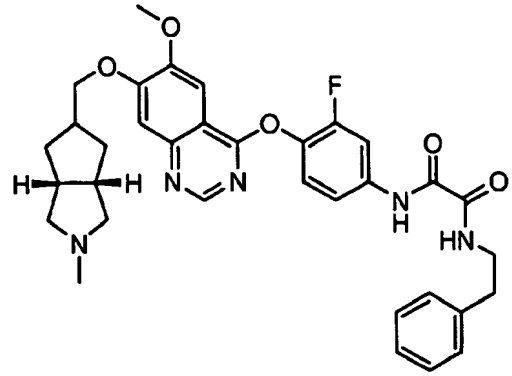
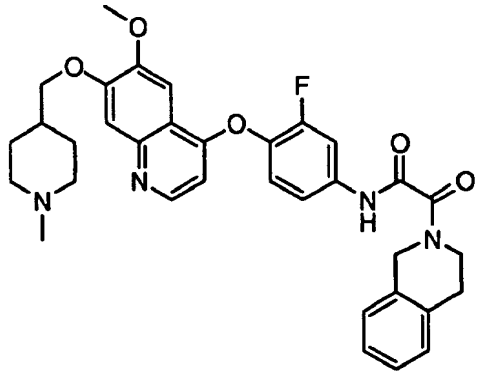
Entry	Name	Structure
141	N-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
142	N-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
143	2-(3,4-Dihydro-1H-isoquinolin-2-yl)-N-{3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-acetamide	

Table 1

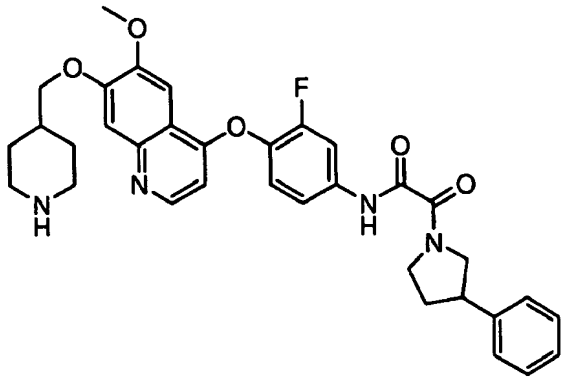
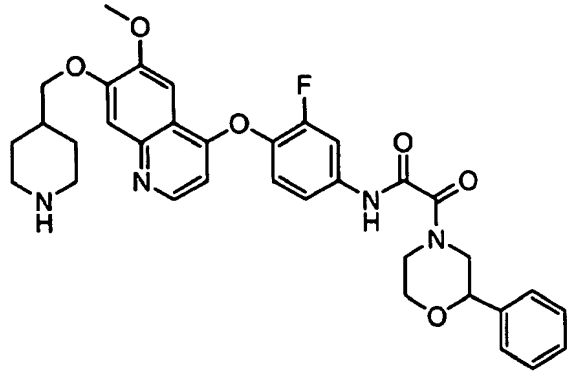
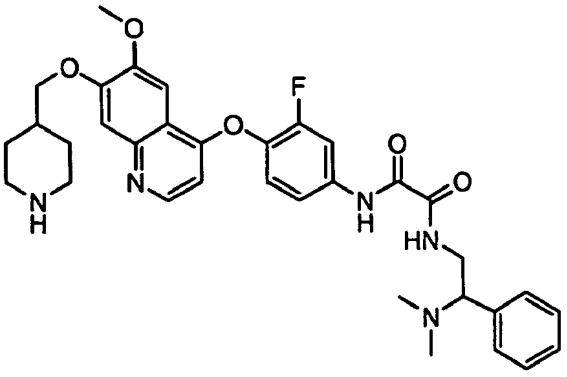
Entry	Name	Structure
144	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-(3-phenyl-pyrrolidin-1-yl)-acetamide	
145	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-(2-phenyl-morpholin-4-yl)-acetamide	
146	N-(2-Dimethylamino-2-phenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

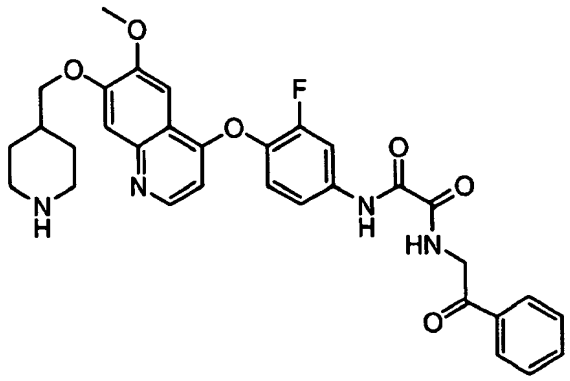
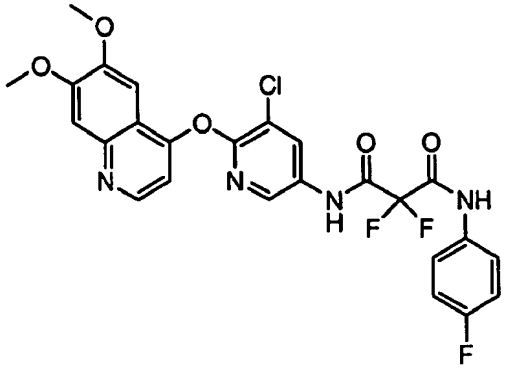
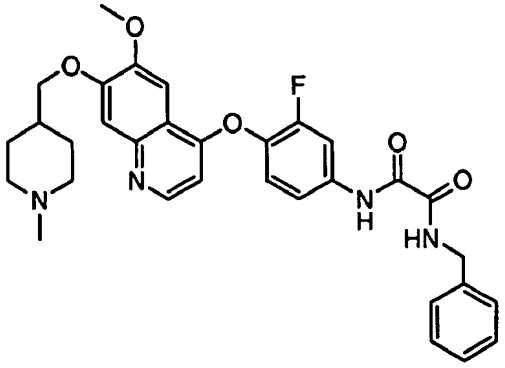
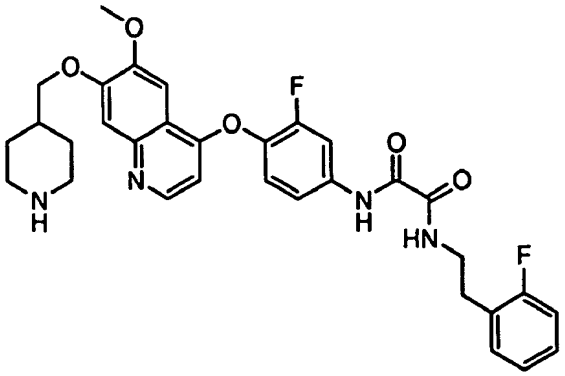
Entry	Name	Structure
147	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-oxo-2-phenyl-ethyl)-oxalamide	
148	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-2,2-difluoro-N'-(4-fluoro-phenyl)-malonamide	
149	N-Benzyl-N'-{3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
150	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-fluoro-phenyl)-ethyl]-oxalamide	

Table 1

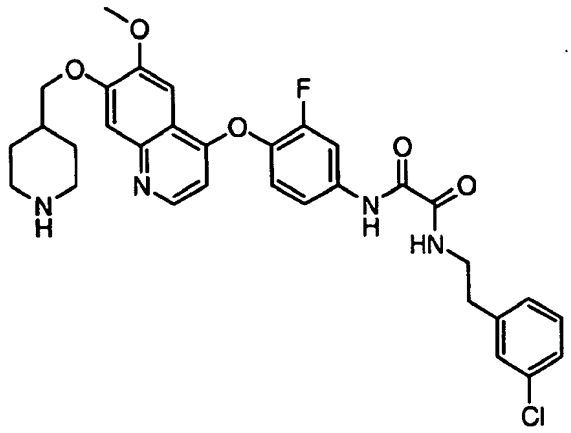
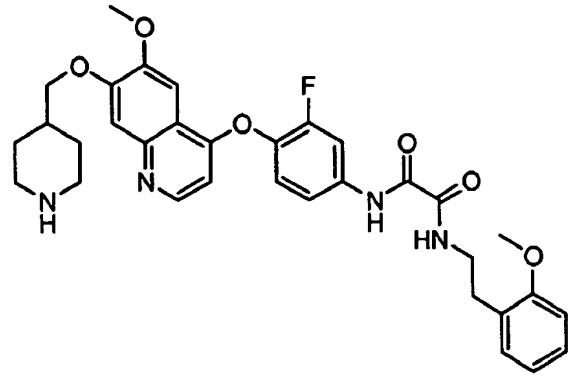
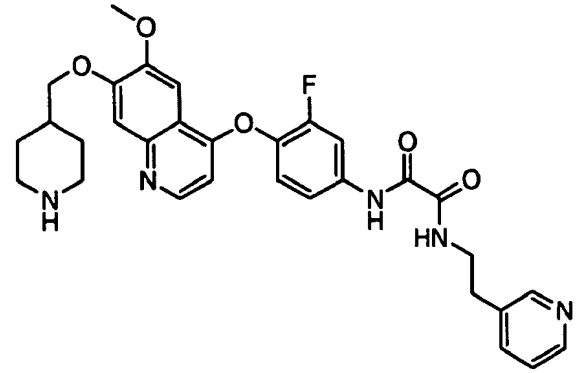
Entry	Name	Structure
151	N-[2-(3-Chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
152	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-methoxy-phenyl)-ethyl]-oxalamide	
153	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-3-yl-ethyl)-oxalamide	

Table 1

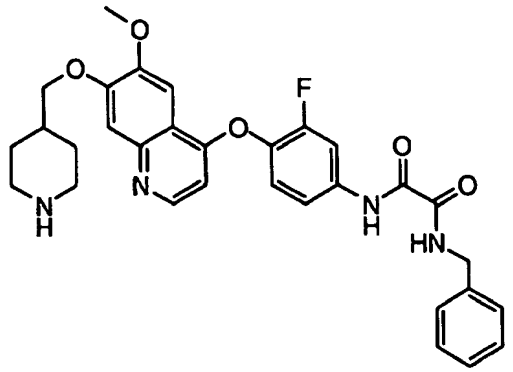
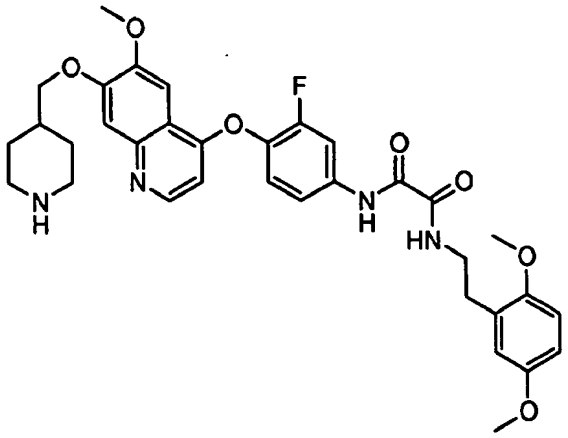
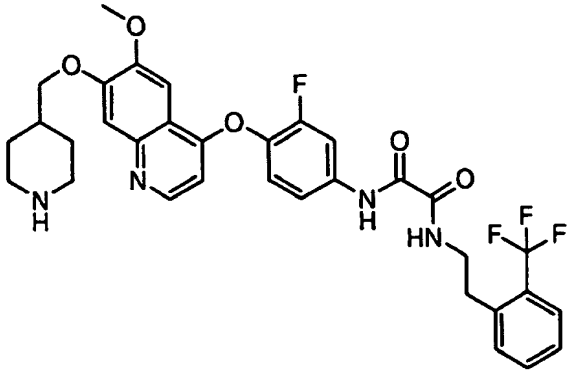
Entry	Name	Structure
154	N-Benzyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
155	N-[2-(2,5-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
156	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-trifluoromethyl-phenyl)-ethyl]-oxalamide	

Table 1

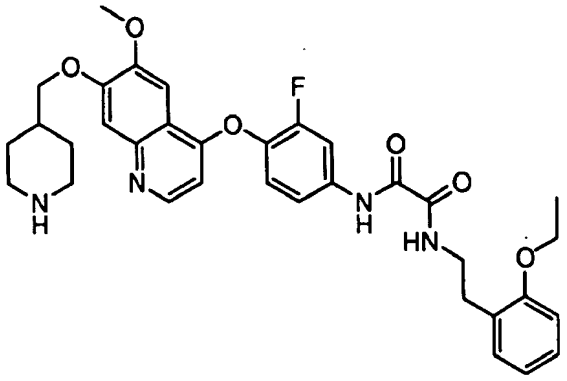
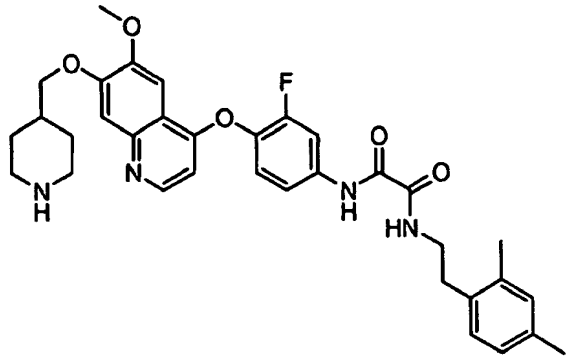
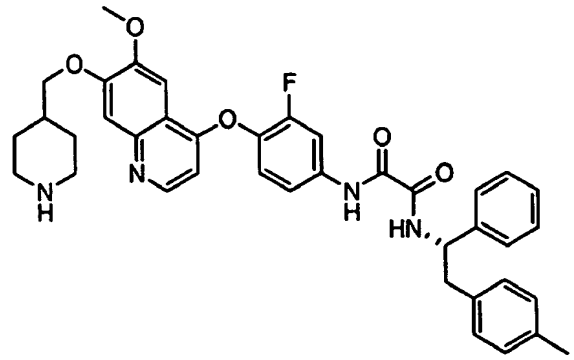
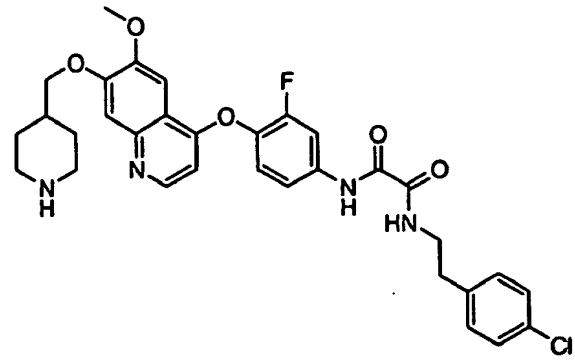
Entry	Name	Structure
157	N-[2-(2-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
158	N-[2-(2,4-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
159	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*S* -phenyl-2-p-tolyl-ethyl)-oxalamide	
160	N-[2-(4-Chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

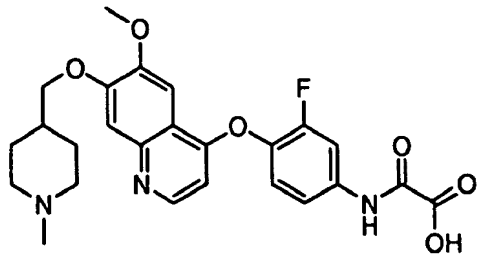
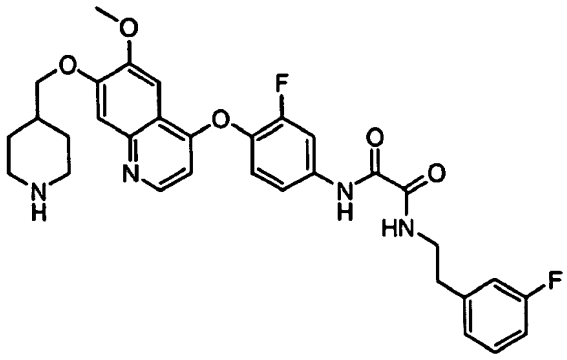
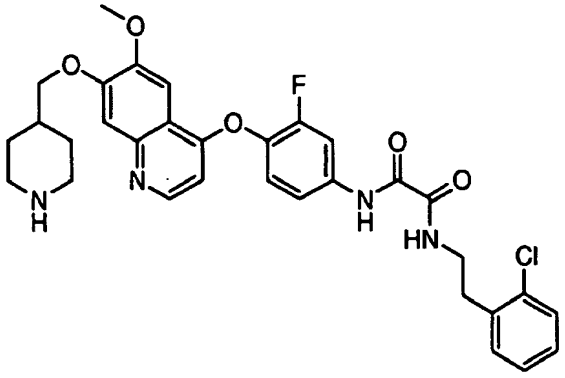
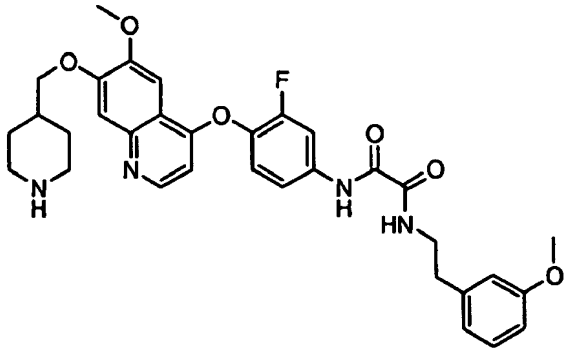
Entry	Name	Structure
161	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamic acid	
162	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-fluoro-phenyl)-ethyl]-oxalamide	
163	N-[2-(2-Chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
164	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-methoxy-phenyl)-ethyl]-oxalamide	

Table 1

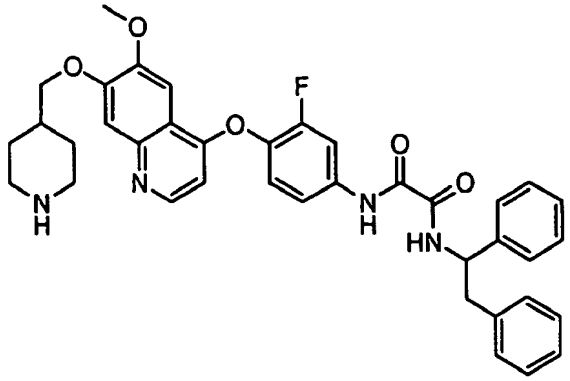
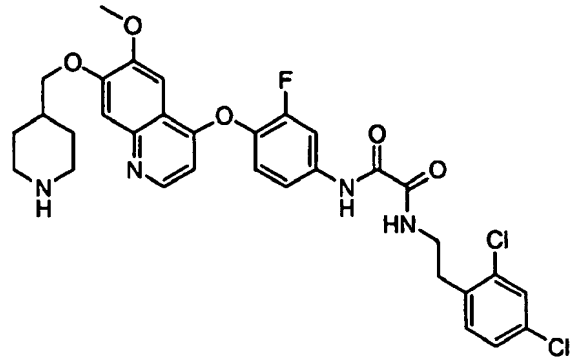
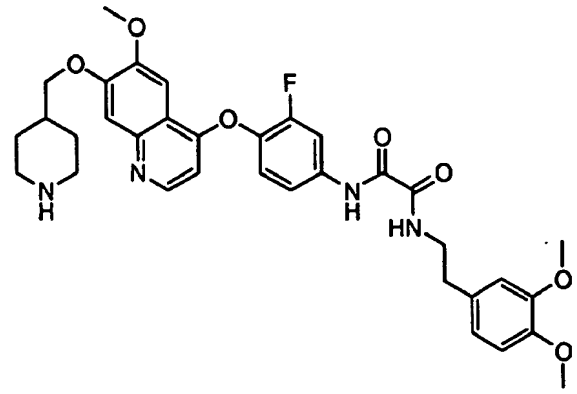
Entry	Name	Structure
165	N-(1,2-Diphenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
166	N-[2-(2,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
167	N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

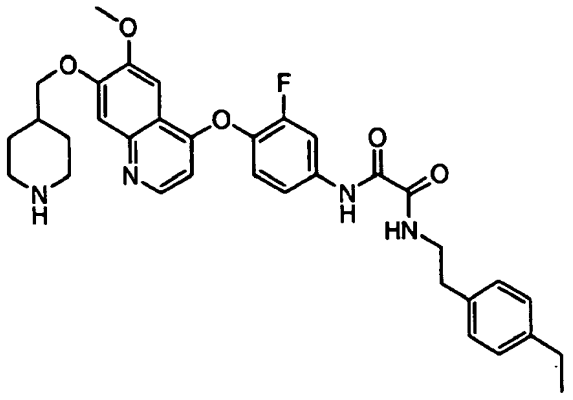
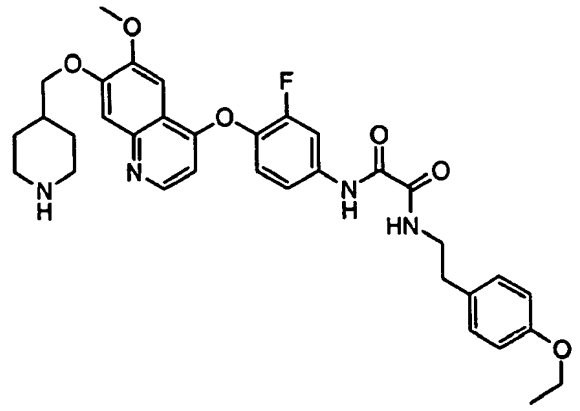
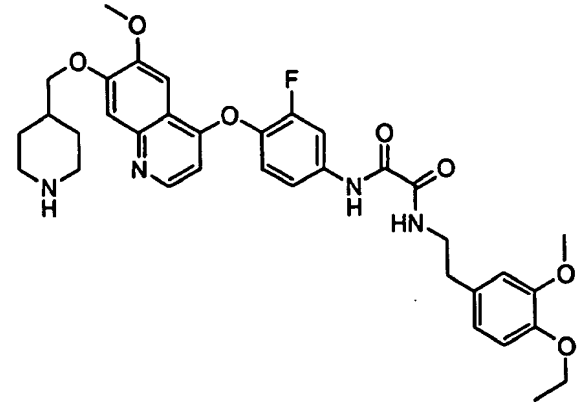
Entry	Name	Structure
168	N-[2-(4-Ethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
169	N-[2-(4-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
170	N-[2-(4-Ethoxy-3-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

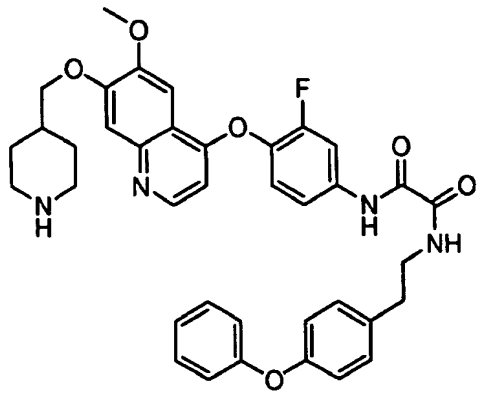
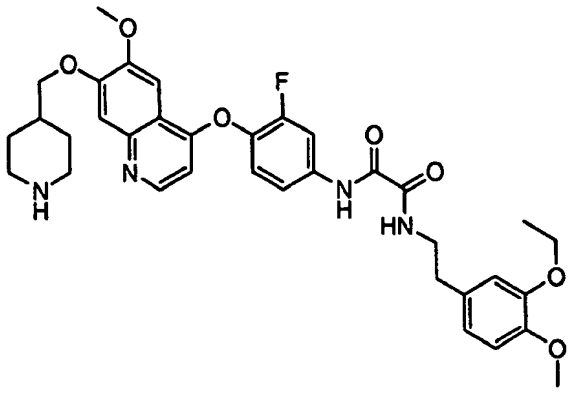
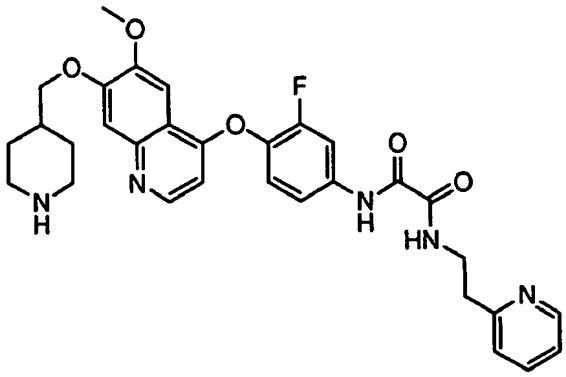
Entry	Name	Structure
171	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-phenoxy-phenyl)-ethyl]-oxalamide	
172	N-[2-(3-Ethoxy-4-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
173	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-2-yl-ethyl)-oxalamide	

Table 1

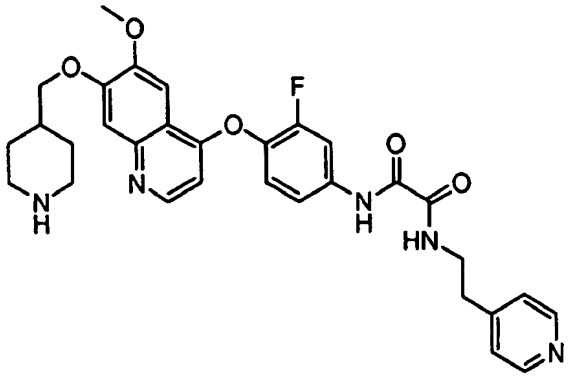
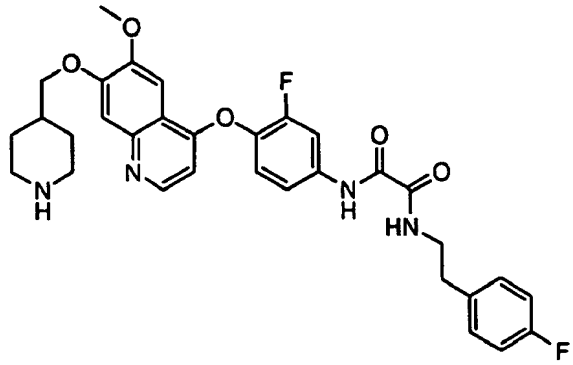
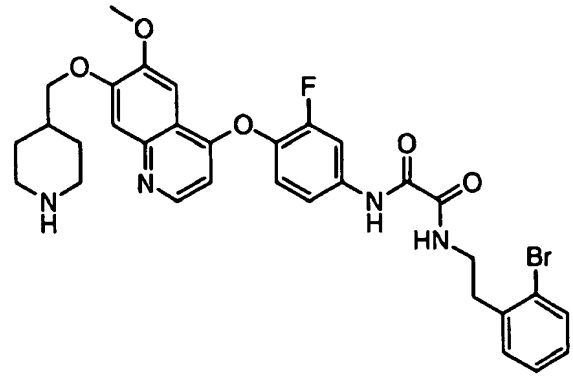
Entry	Name	Structure
174	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-4-yl-ethyl)-oxalamide	
175	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-fluoro-phenyl)-ethyl]-oxalamide	
176	N-[2-(2-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

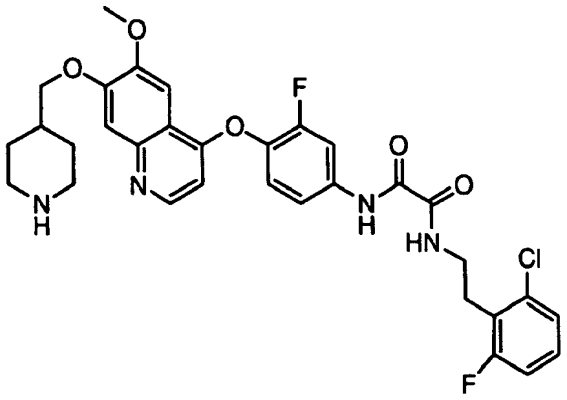
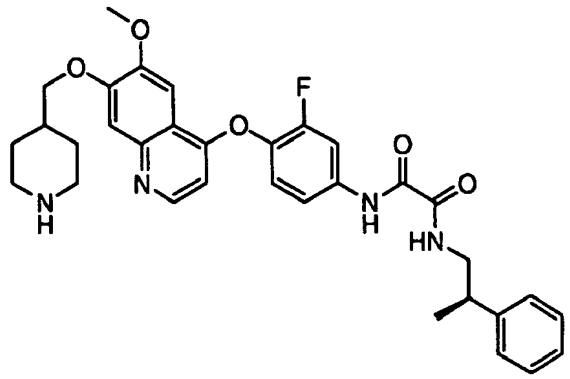
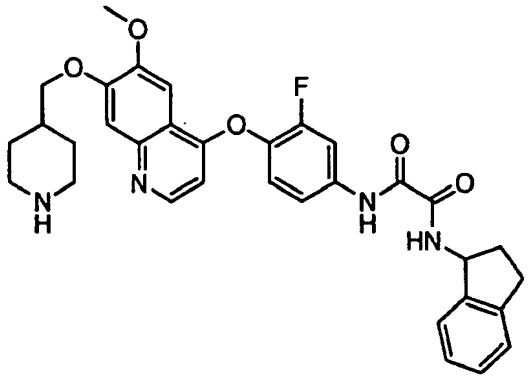
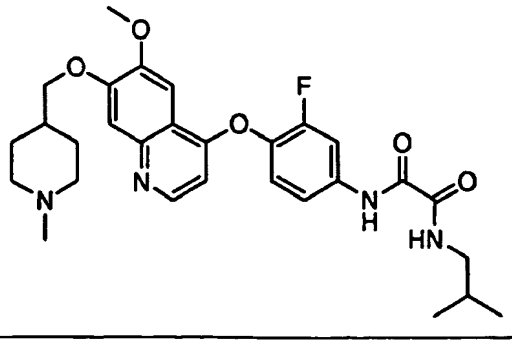
Entry	Name	Structure
177	N-[2-(2-Chloro-6-fluoro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
178	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2*R*-phenyl-propyl)-oxalamide	
179	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-indan-1-yl-oxalamide	
180	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-isobutyl-oxalamide	

Table 1

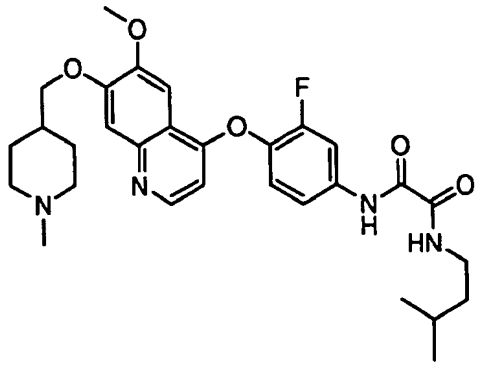
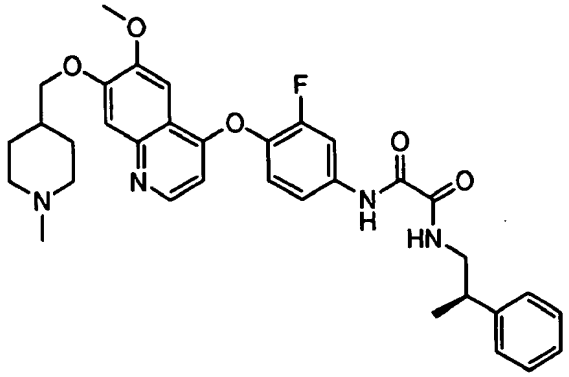
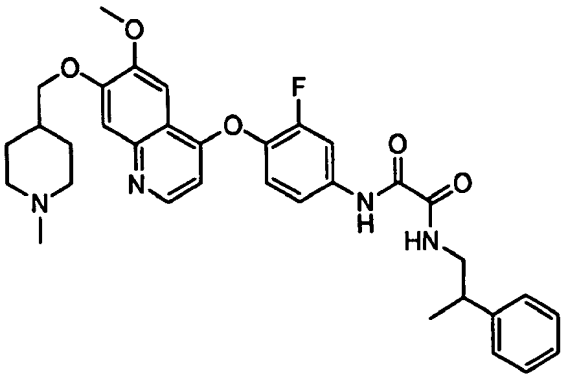
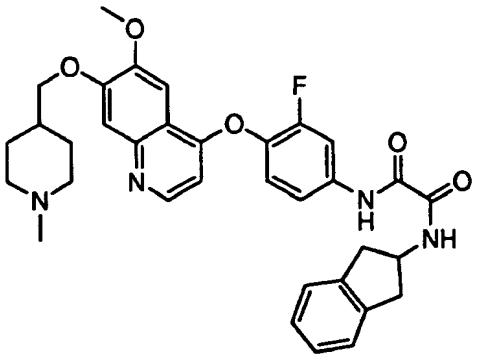
Entry	Name	Structure
181	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-butyl)-oxalamide	
182	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2*R*-phenyl-propyl)-oxalamide	
183	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-phenyl-propyl)-oxalamide	
184	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-indan-2-yl-oxalamide	

Table 1

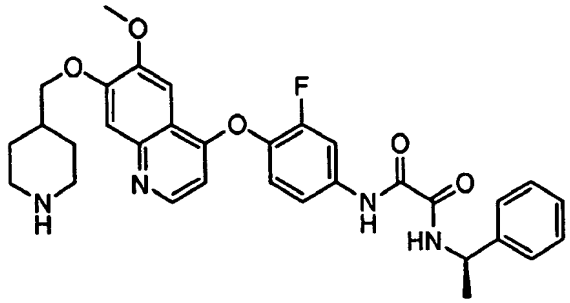
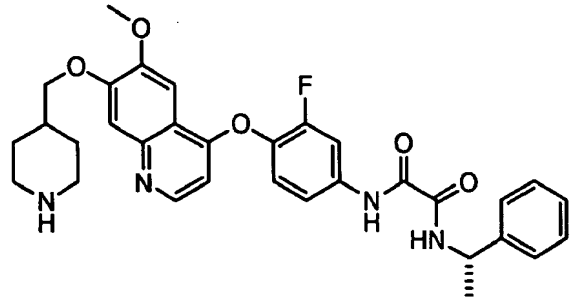
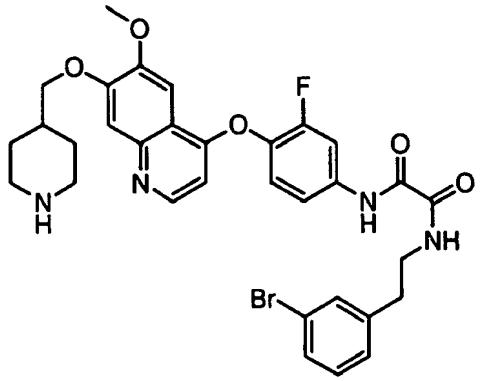
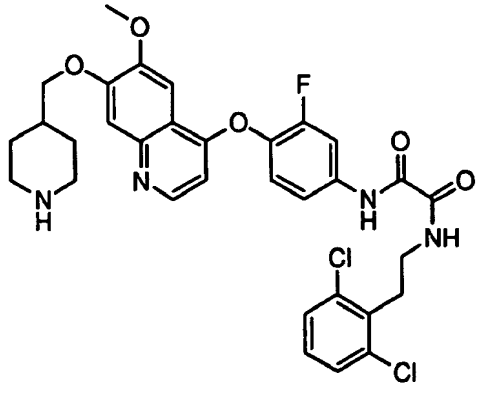
Entry	Name	Structure
185	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*R*-phenyl-ethyl)-oxalamide	
186	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*S*-phenyl-ethyl)-oxalamide	
187	N-[2-(3-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
188	N-[2-(2,6-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

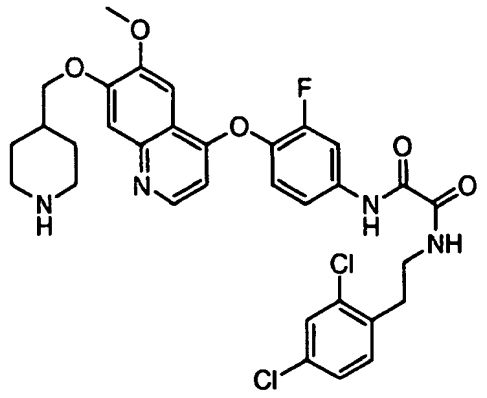
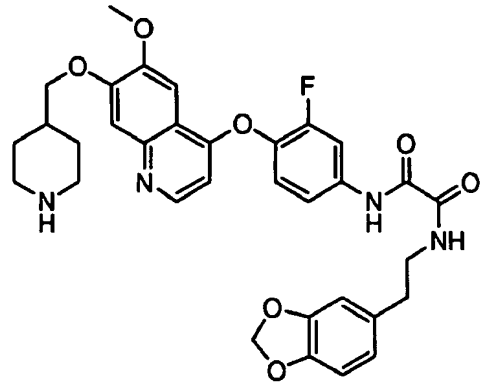
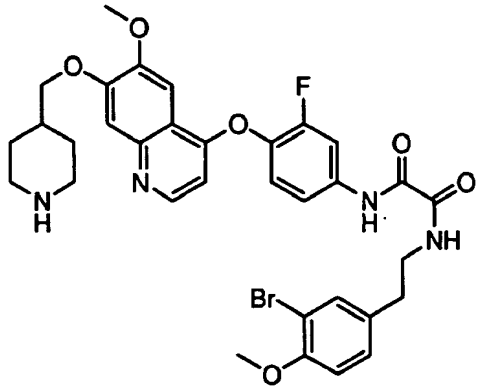
Entry	Name	Structure
189	N-[2-(2,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
190	N-(2-Benzo[1,3]dioxol-5-yl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
192	N-[2-(3-Bromo-4-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

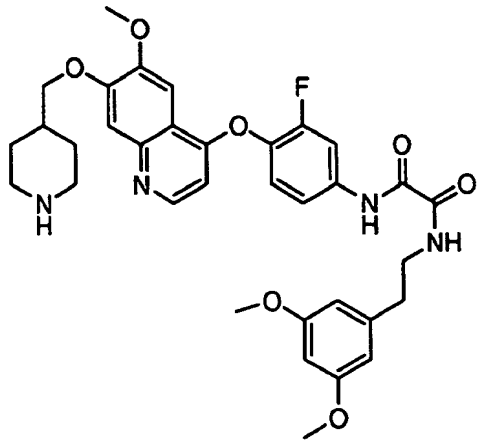
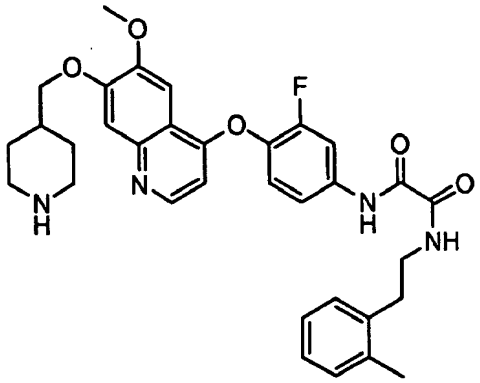
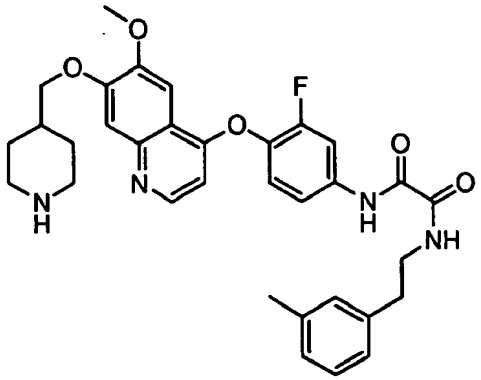
Entry	Name	Structure
193	N-[2-(3,5-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
194	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-o-tolyl-ethyl)-oxalamide	
195	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-m-tolyl-ethyl)-oxalamide	

Table 1

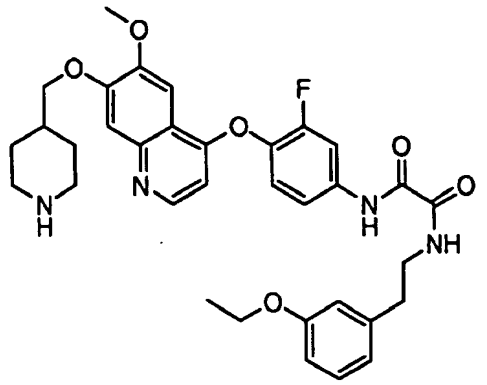
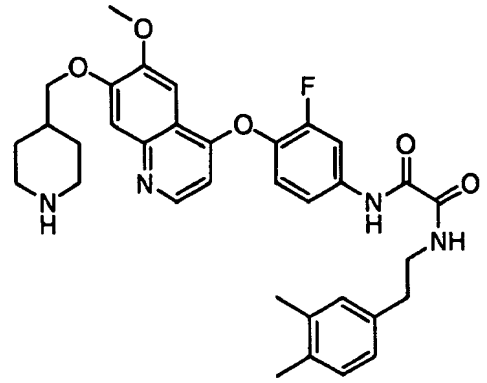
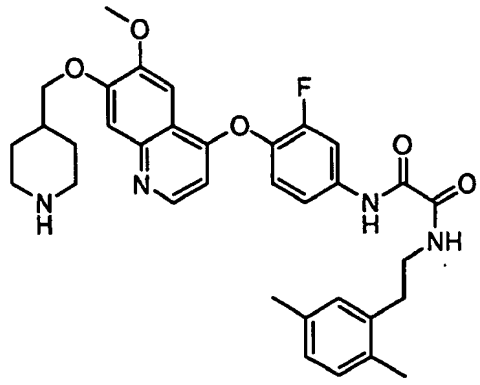
Entry	Name	Structure
196	N-[2-(3-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
197	N-[2-(3,4-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
198	N-[2-(2,5-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

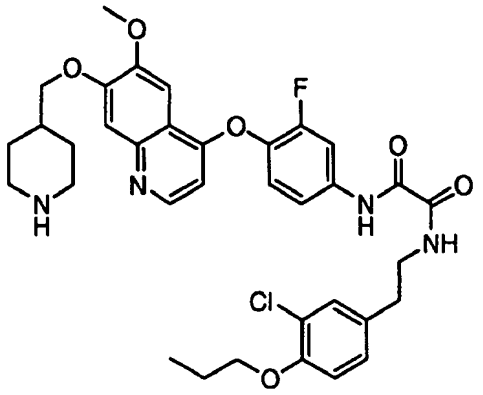
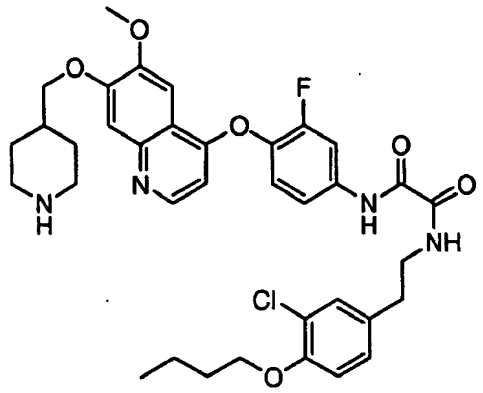
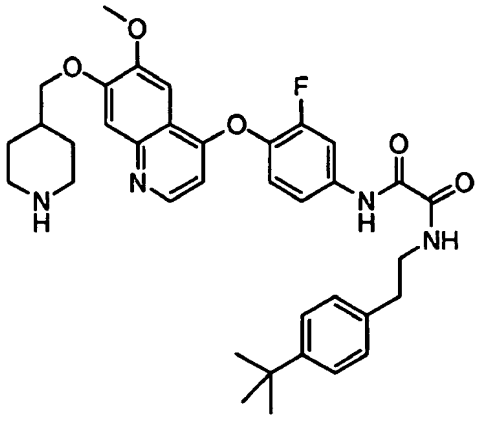
Entry	Name	Structure
199	N-[2-(3-Chloro-4-propoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
200	N-[2-(4-Butoxy-3-chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
201	N-[2-(4-tert-Butyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

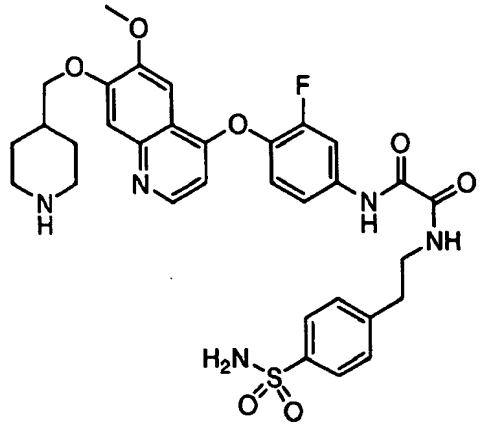
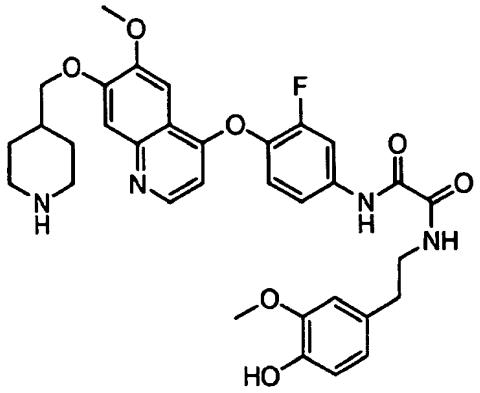
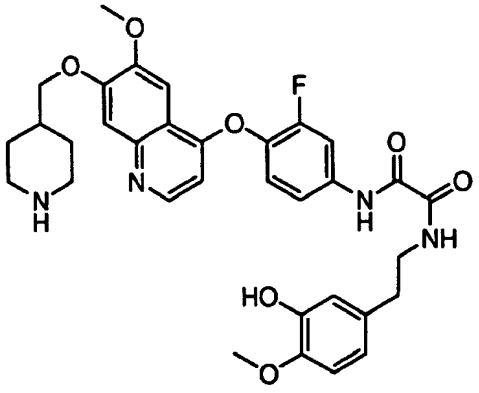
Entry	Name	Structure
202	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-sulfamoyl-phenyl)-ethyl]-oxalamide	
203	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-hydroxy-3-methoxy-phenyl)-ethyl]-oxalamide	
204	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-hydroxy-4-methoxy-phenyl)-ethyl]-oxalamide	

Table 1

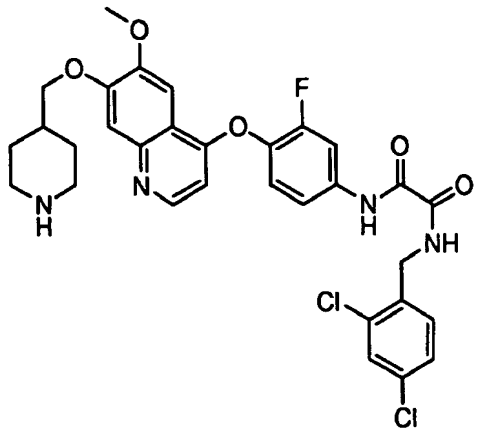
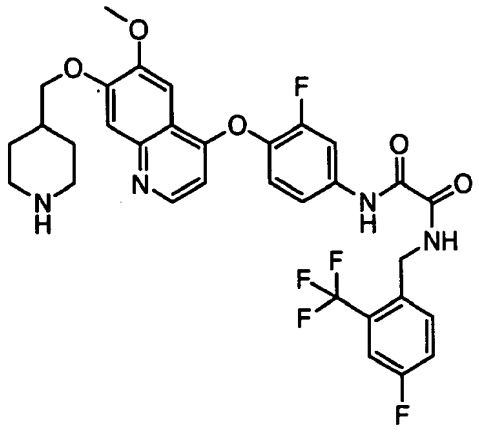
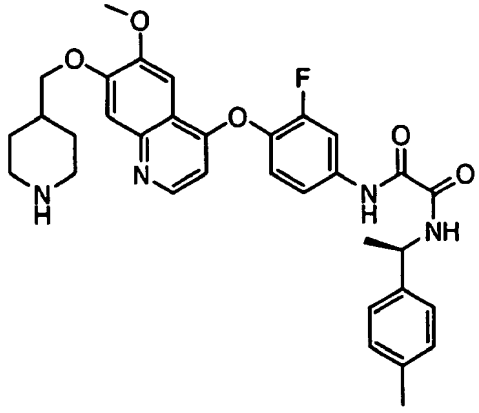
Entry	Name	Structure
205	N-(2,4-Dichloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
206	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-fluoro-2-trifluoromethyl-benzyl)-oxalamide	
207	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-p-tolyl-ethyl)-oxalamide	

Table 1

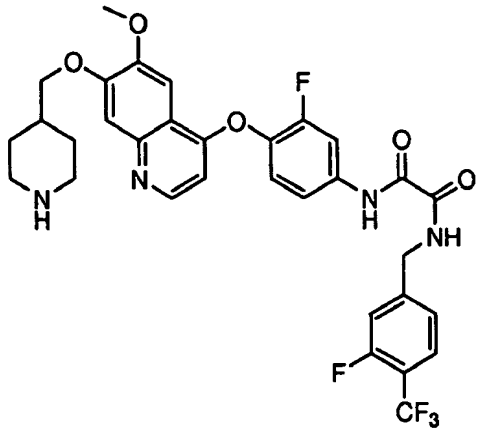
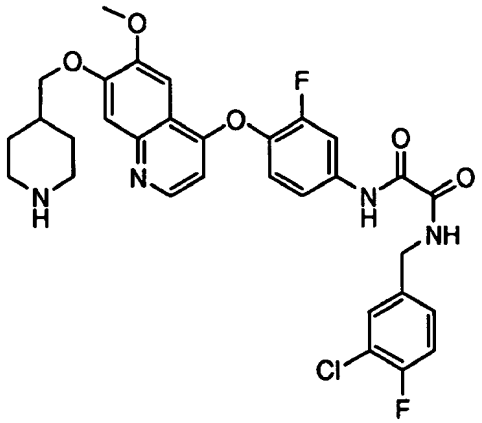
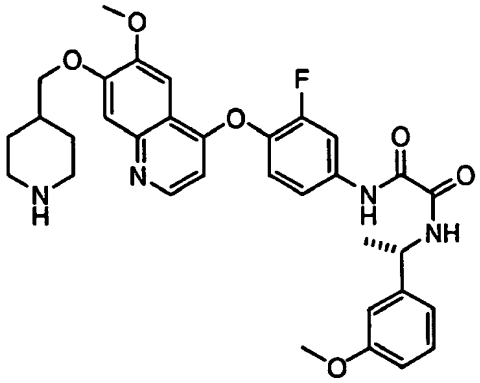
Entry	Name	Structure
208	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-fluoro-4-trifluoromethyl-benzyl)-oxalamide	
209	N-(3-Chloro-4-fluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
210	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[1-(3-methoxy-phenyl)-ethyl]-oxalamide	

Table 1

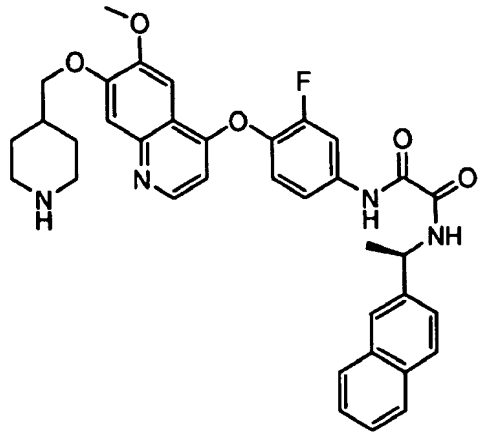
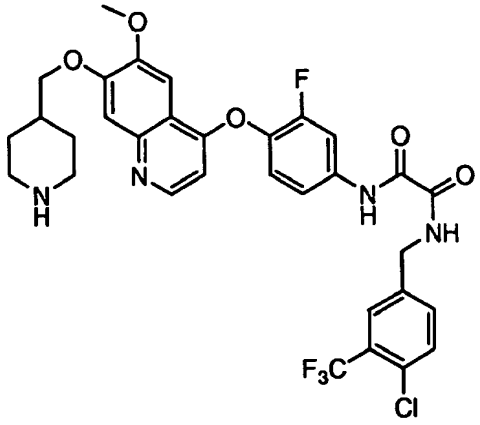
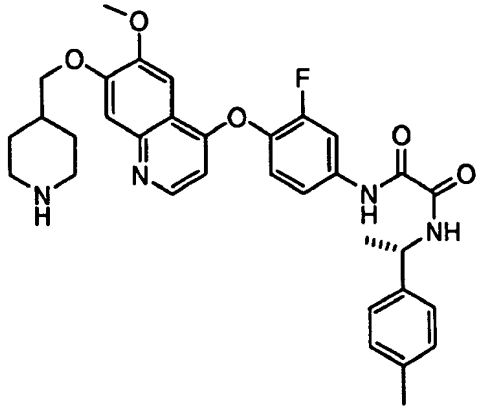
Entry	Name	Structure
211	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-naphthalen-2-yl-ethyl)-oxalamide	
212	N-(4-Chloro-3-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
213	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-p-tolyl-ethyl)-oxalamide	

Table 1

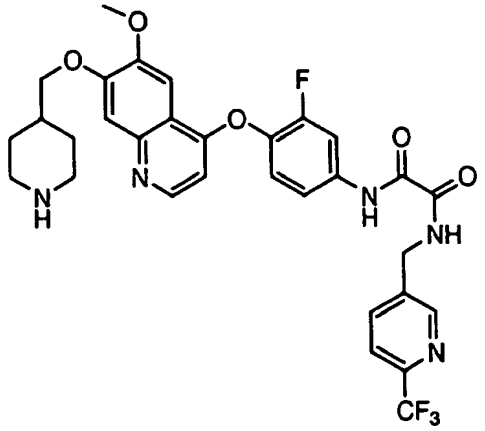
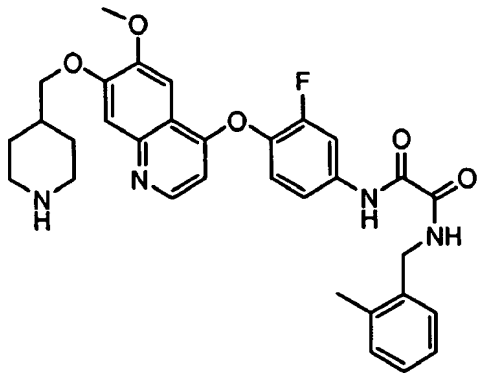
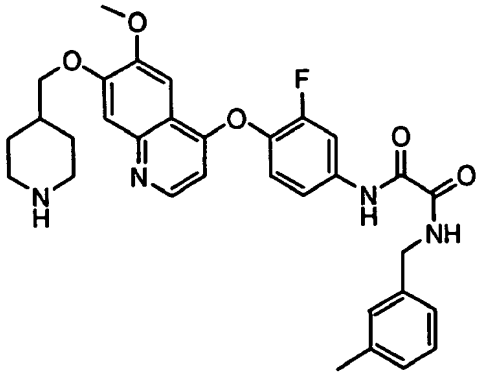
Entry	Name	Structure
214	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(6-trifluoromethyl-pyridin-3-ylmethyl)-oxalamide	
215	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-methyl-benzyl)-oxalamide	
216	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-benzyl)-oxalamide	

Table 1

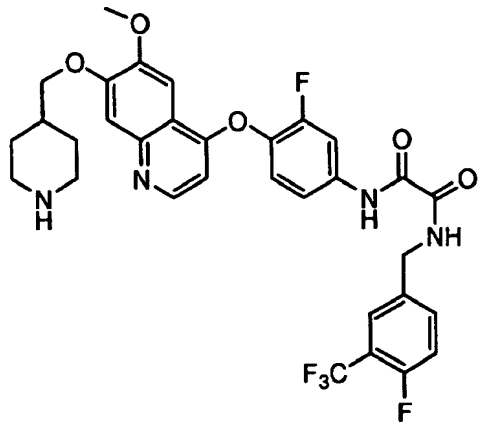
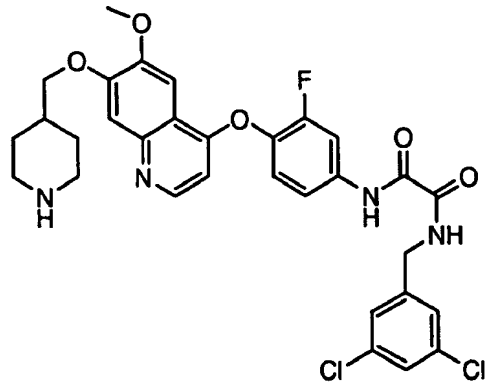
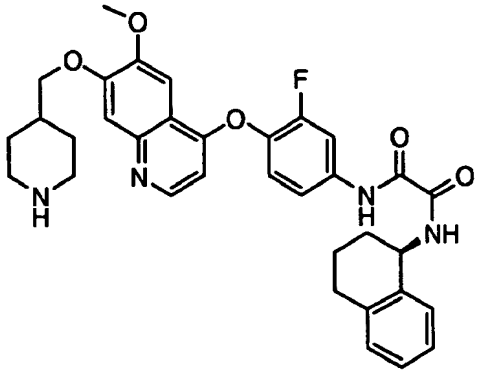
Entry	Name	Structure
217	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-fluoro-3-trifluoromethyl-benzyl)-oxalamide	
218	N-(3,5-Dichloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
219	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R,2,3,4-tetrahydro-naphthalen-1-yl)-oxalamide	

Table 1

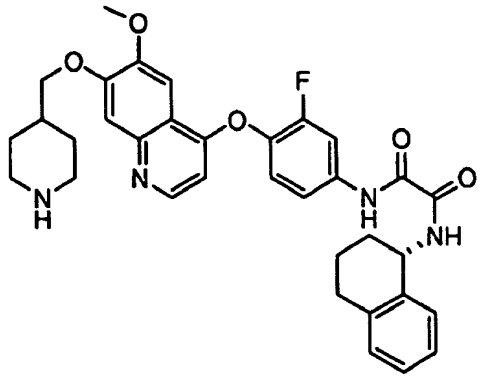
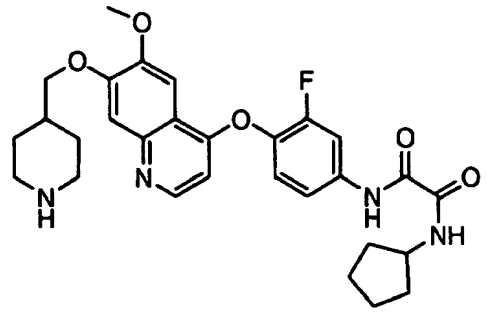
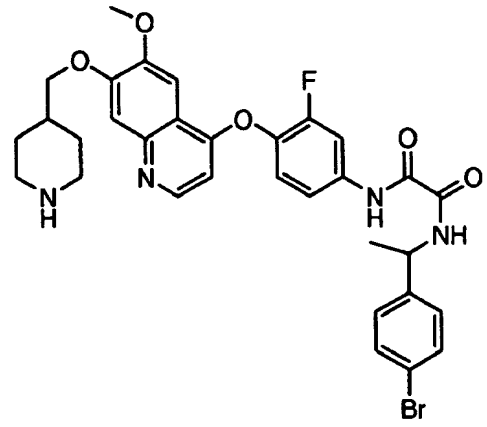
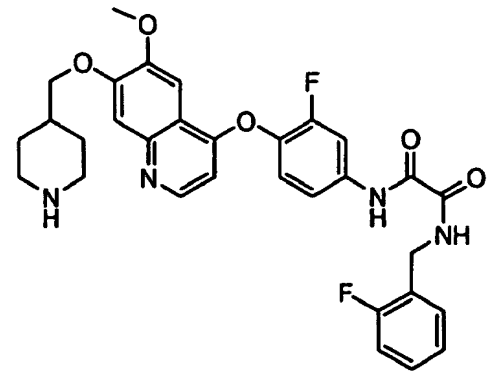
Entry	Name	Structure
220	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1S,2,3,4-tetrahydro-naphthalen-1-yl)-oxalamide	
221	N-Cyclopentyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
222	N-[1-(4-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
223	N-(2-Fluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

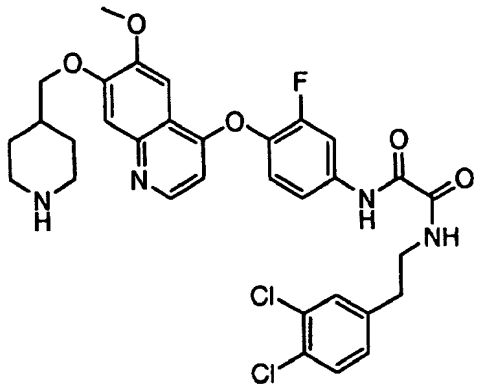
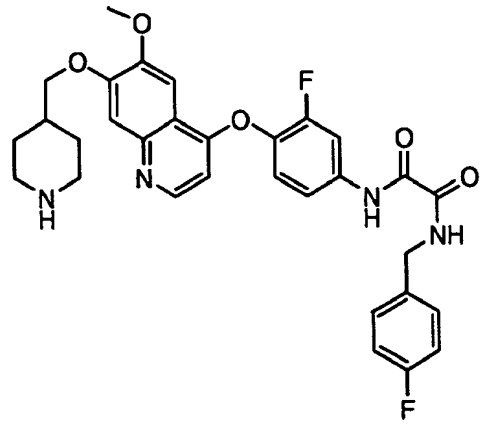
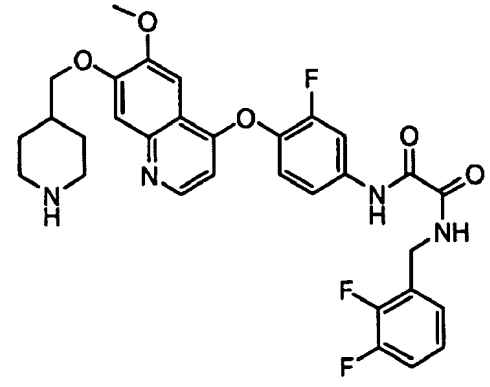
Entry	Name	Structure
224	N-[2-(3,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
225	N-(4-Fluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
226	N-(2,3-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

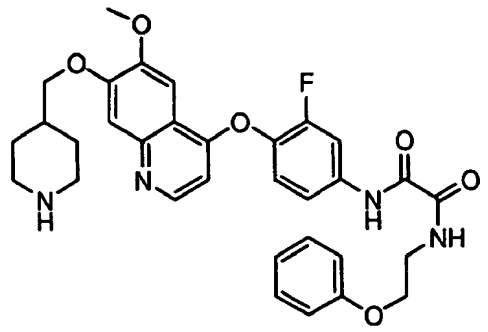
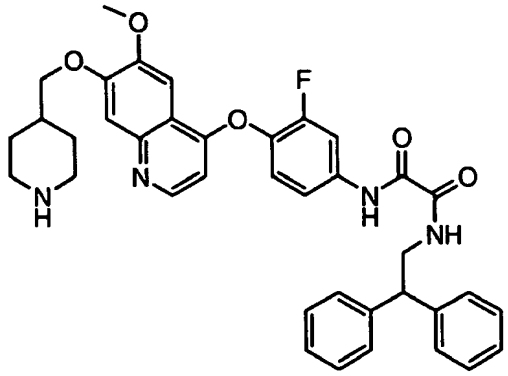
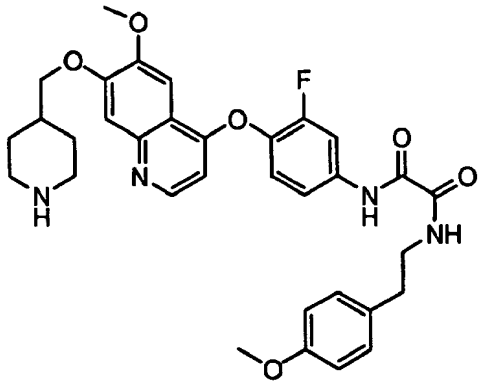
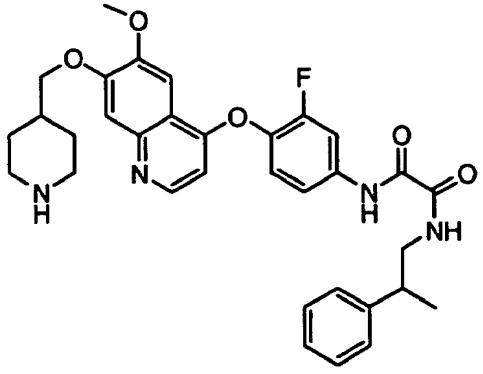
Entry	Name	Structure
227	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-phenoxy-ethyl)-oxalamide	
228	N-(2,2-Diphenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
229	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-methoxy-phenyl)-ethyl]-oxalamide	
230	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-phenyl-propyl)-oxalamide	

Table 1

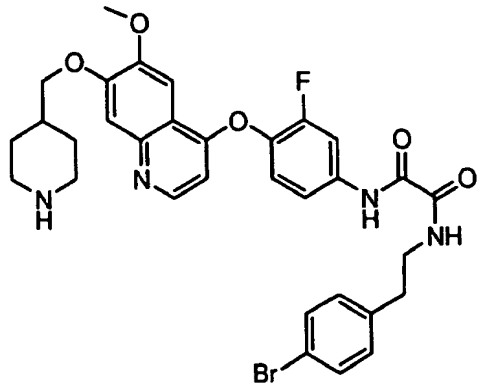
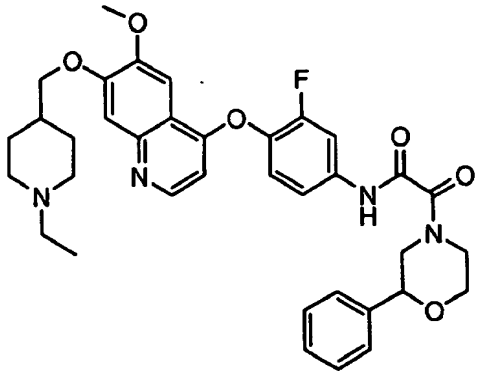
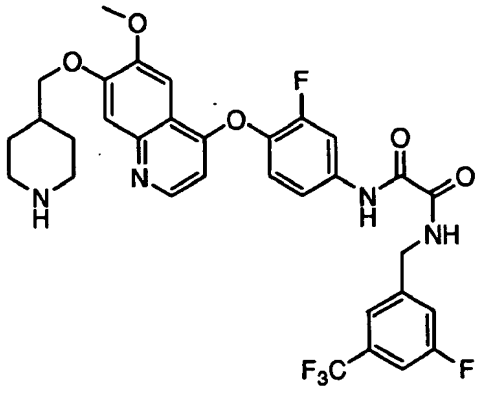
Entry	Name	Structure
231	N-[2-(4-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
232	N-{4-[7-(1-Ethyl-piperidin-4-ylmethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-2-oxo-2-(2-phenyl-morpholin-4-yl)-acetamide	
233	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-fluoro-5-trifluoromethyl-benzyl)-oxalamide	

Table 1

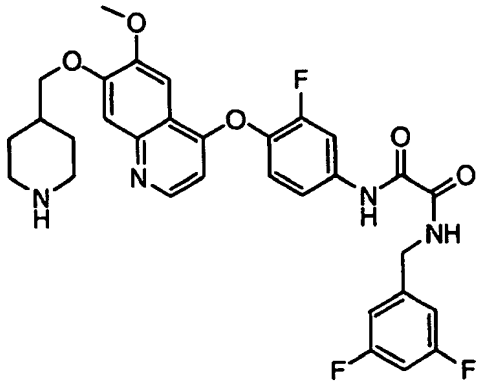
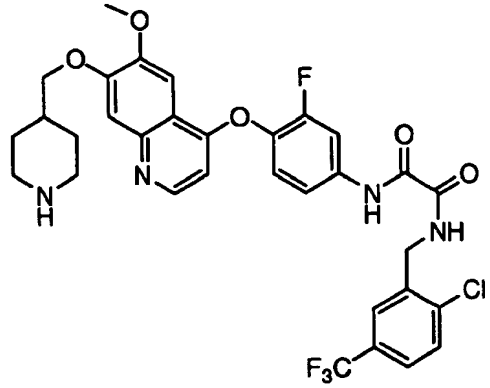
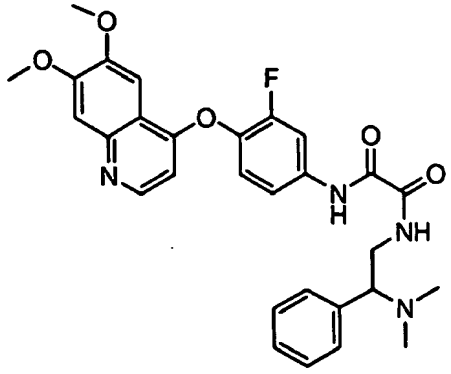
Entry	Name	Structure
234	N-(3,5-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
235	N-(2-Chloro-5-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
236	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-dimethylamino-2-phenyl-ethyl)-oxalamide	

Table 1

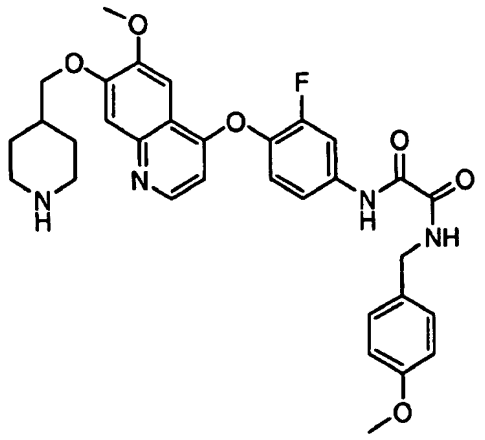
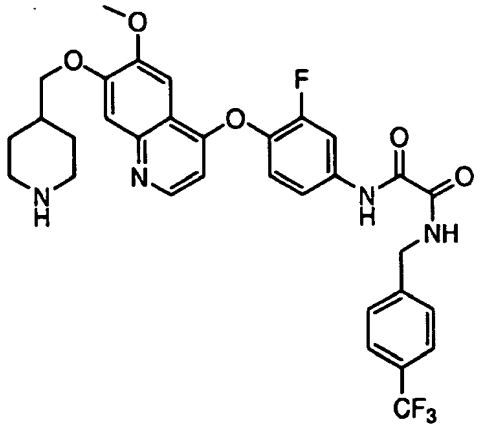
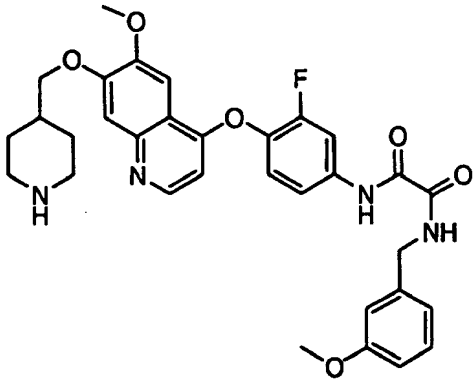
Entry	Name	Structure
237	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-methoxy-benzyl)-oxalamide	
238	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethyl-benzyl)-oxalamide	
239	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methoxy-benzyl)-oxalamide	

Table 1

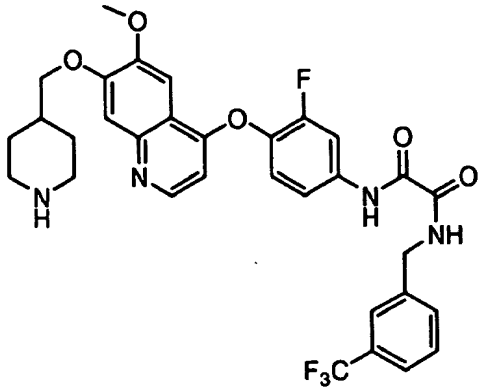
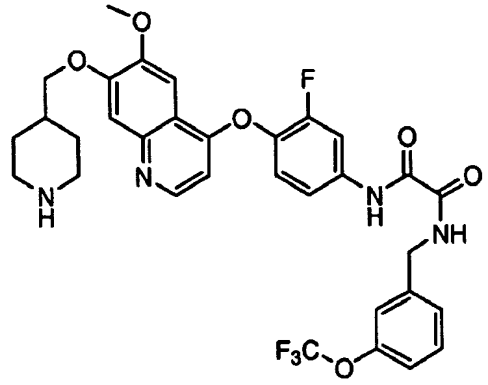
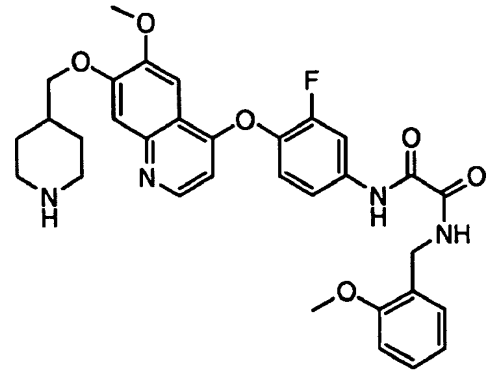
Entry	Name	Structure
240	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-trifluoromethyl-benzyl)-oxalamide	
241	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-trifluoromethoxy-benzyl)-oxalamide	
242	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-methoxy-benzyl)-oxalamide	

Table 1

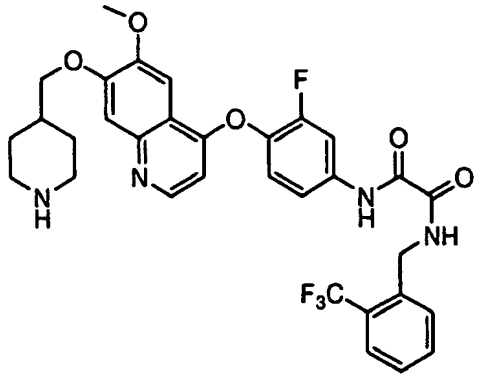
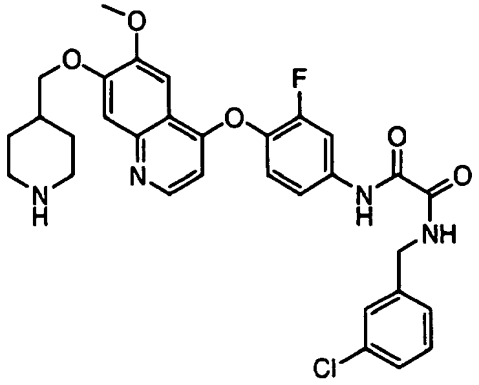
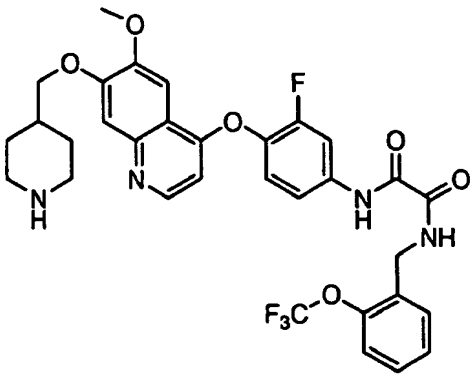
Entry	Name	Structure
243	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-trifluoromethyl-benzyl)-oxalamide	
244	N-(3-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
245	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-trifluoromethoxy-benzyl)-oxalamide	

Table 1

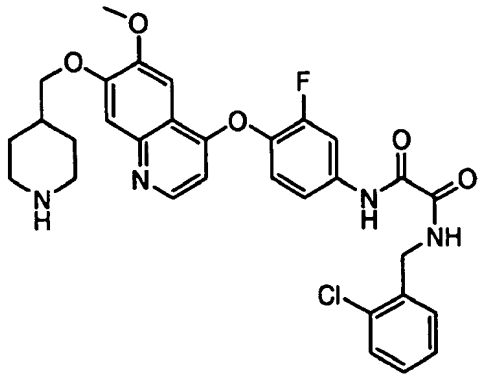
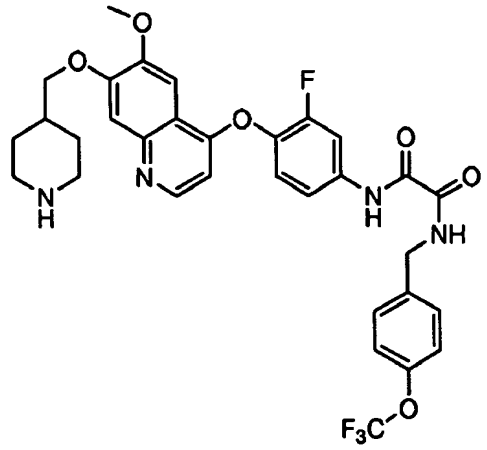
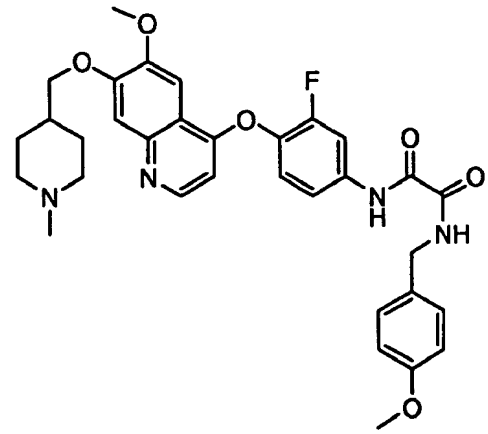
Entry	Name	Structure
246	N-(2-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
247	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethoxy-benzyl)-oxalamide	
248	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-methoxy-benzyl)-oxalamide	

Table 1

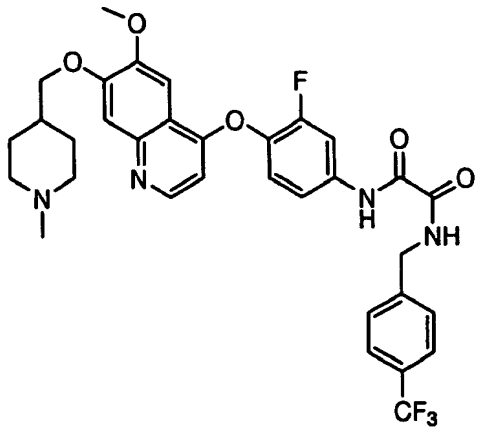
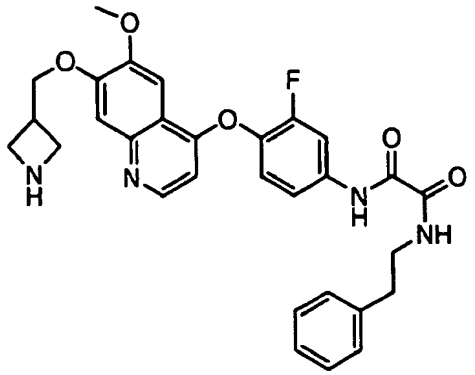
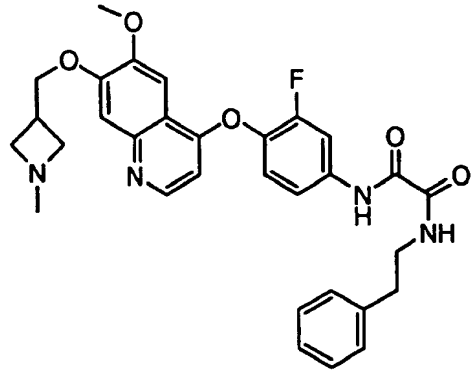
Entry	Name	Structure
249	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethyl-benzyl)-oxalamide	
250	N-{4-[7-(Azetidin-3-ylmethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide	
251	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-azetidin-3-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	

Table 1

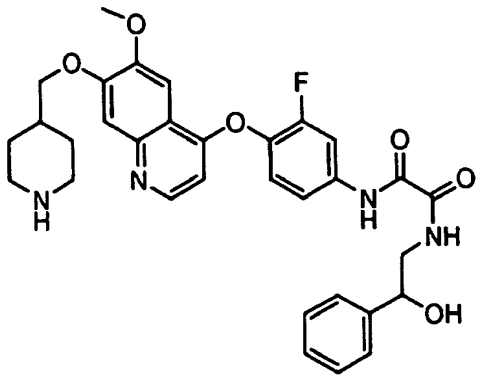
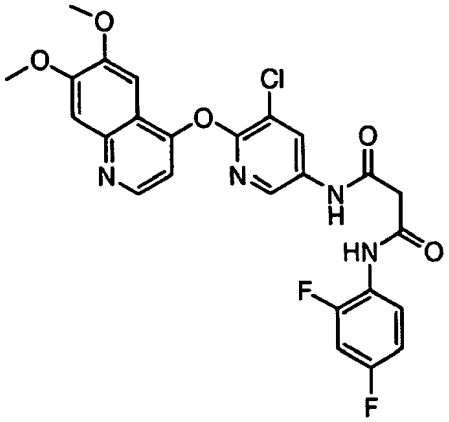
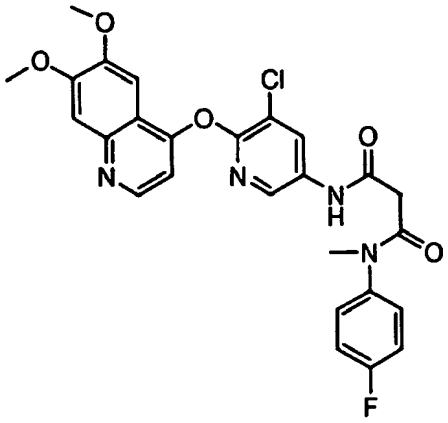
Entry	Name	Structure
252	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-hydroxy-2-phenyl-ethyl)-oxalamide	
253	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(2,4-difluoro-phenyl)-malonamide	
254	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(4-fluoro-phenyl)-N'-methyl-malonamide	

Table 1

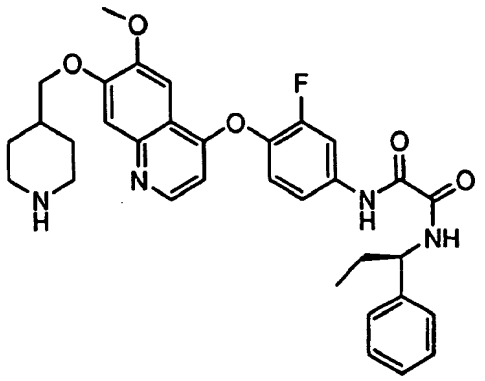
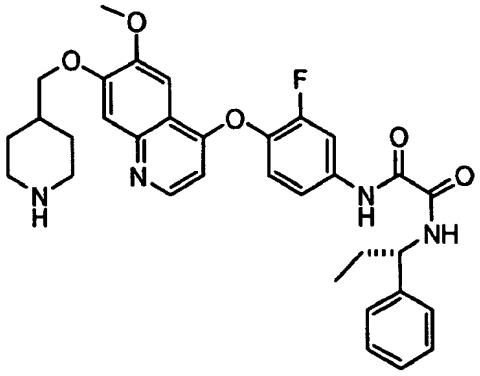
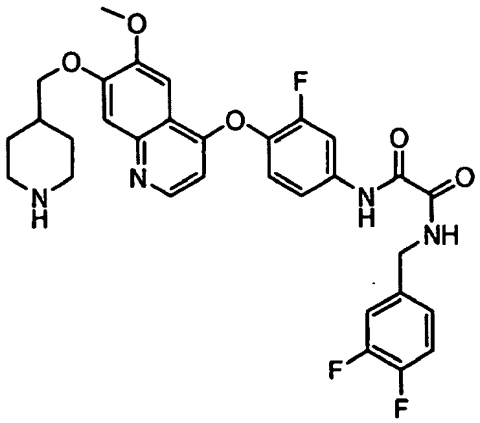
Entry	Name	Structure
255	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R-phenyl-propyl)-oxalamide	
256	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R-phenyl-propyl)-oxalamide	
257	N-(3,4-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

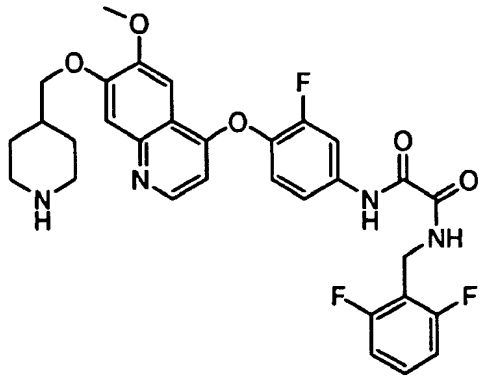
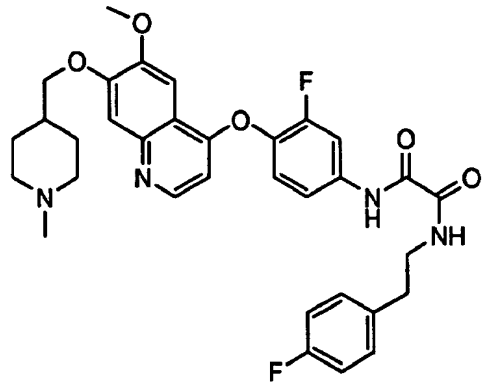
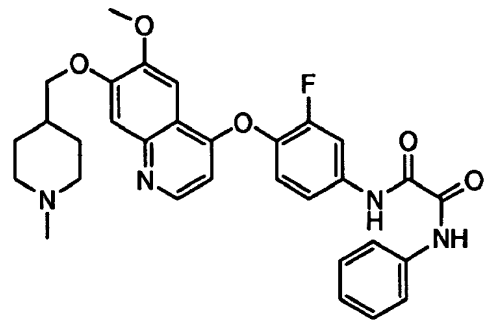
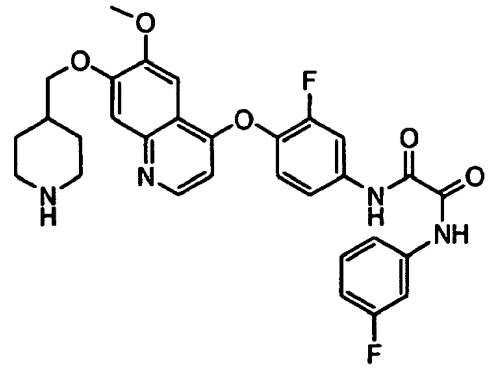
Entry	Name	Structure
258	N-(2,6-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
259	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-fluoro-phenyl)-ethyl]-oxalamide	
260	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenyl-oxalamide	
261	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-fluoro-phenyl)-oxalamide	

Table 1

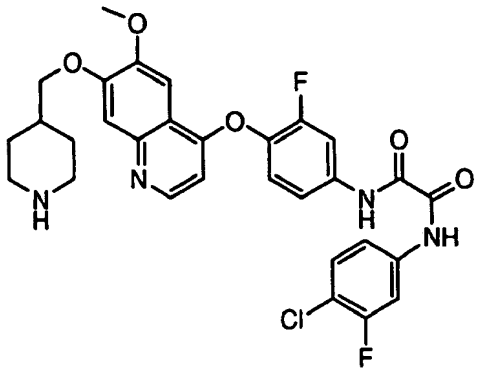
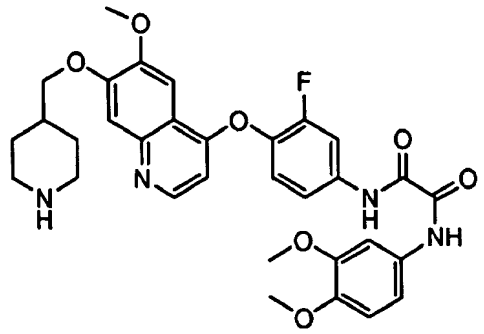
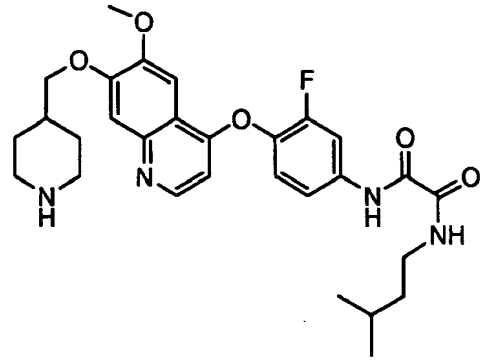
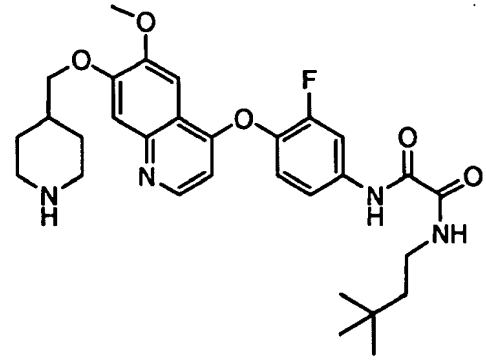
Entry	Name	Structure
262	N-(4-Chloro-3-fluoro-phenyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
263	N-(3,4-Dimethoxy-phenyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
264	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-butyl)-oxalamide	
265	N-(3,3-Dimethyl-butyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

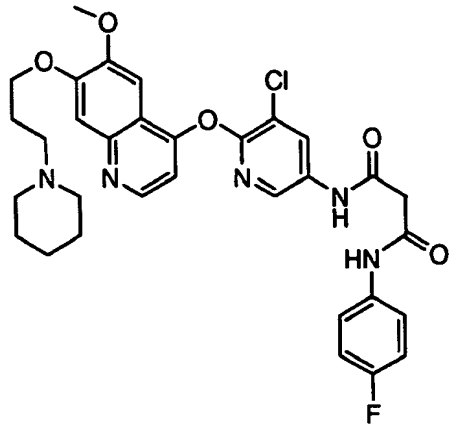
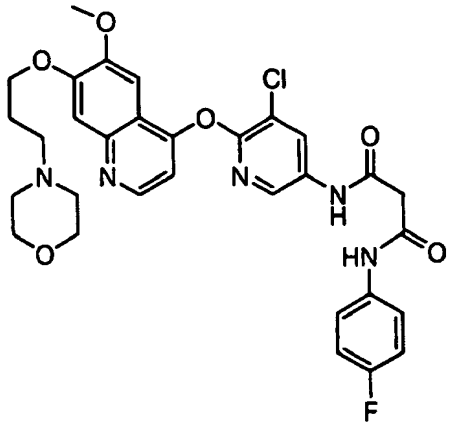
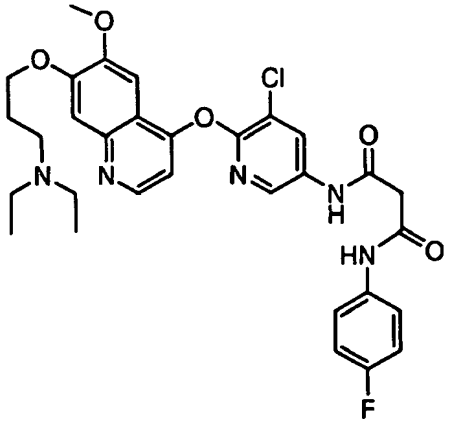
Entry	Name	Structure
266	N-{5-Chloro-6-[6-methoxy-7-(3-piperidin-1-yl-propoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	
267	N-{5-Chloro-6-[6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	
268	N-{5-Chloro-6-[7-(3-diethylamino-propoxy)-6-methoxy-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	

Table 1

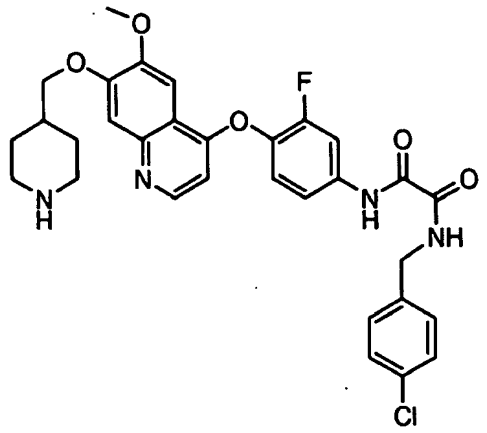
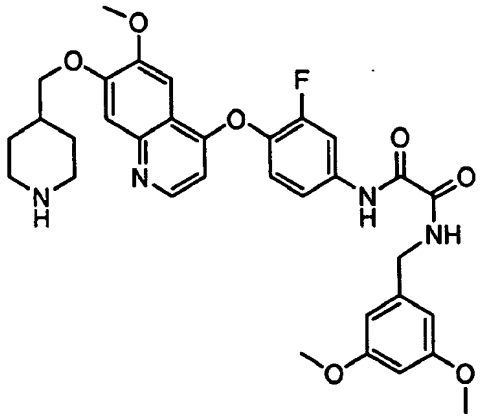
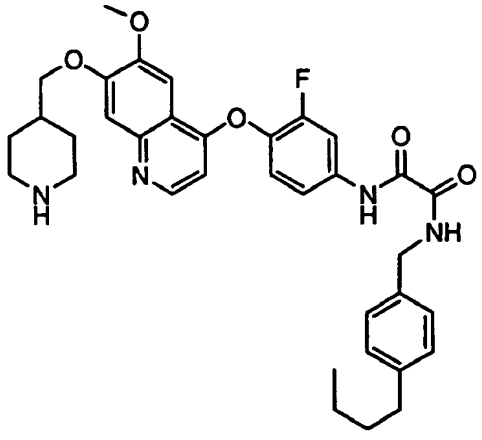
Entry	Name	Structure
269	N-(4-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
270	N-(3,5-Dimethoxy-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
271	N-(4-Butyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

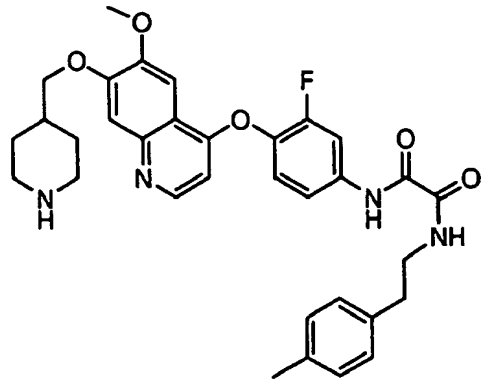
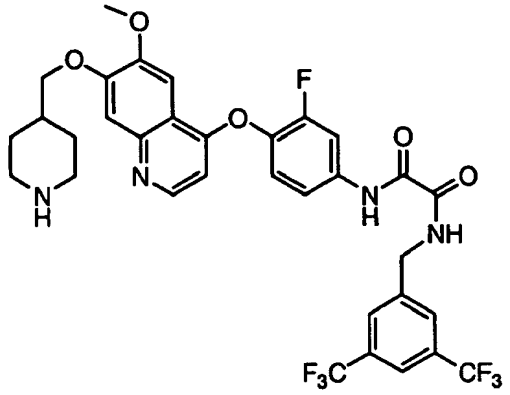
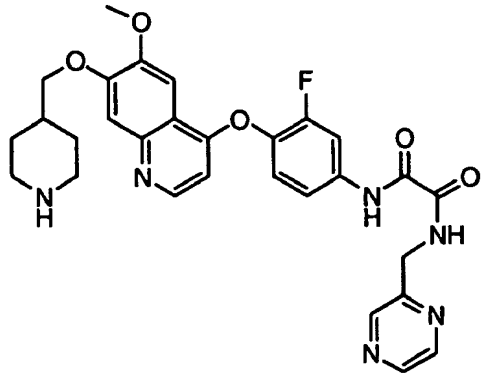
Entry	Name	Structure
272	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-p-tolyl-ethyl)-oxalamide	
273	N-(3,5-Bis-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
274	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-pyrazin-2-ylmethyl-oxalamide	

Table 1

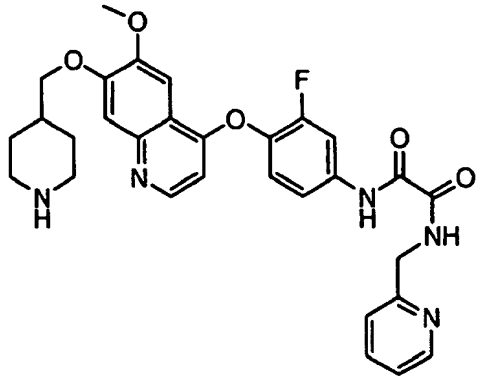
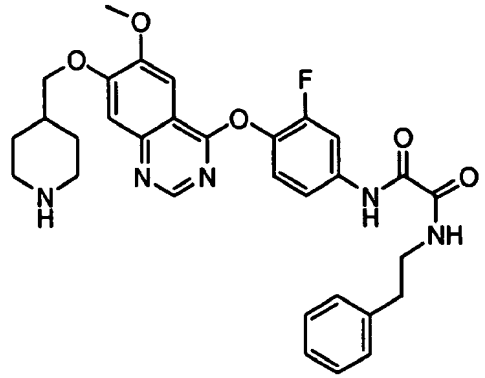
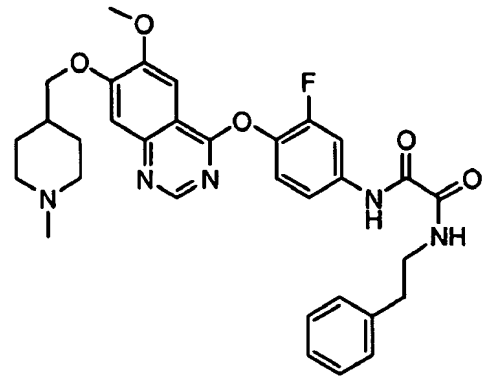
Entry	Name	Structure
275	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-pyridin-2-ylmethyl-oxalamide	
276	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
277	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	

Table 1

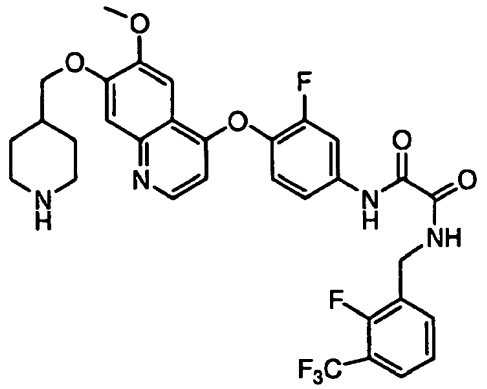
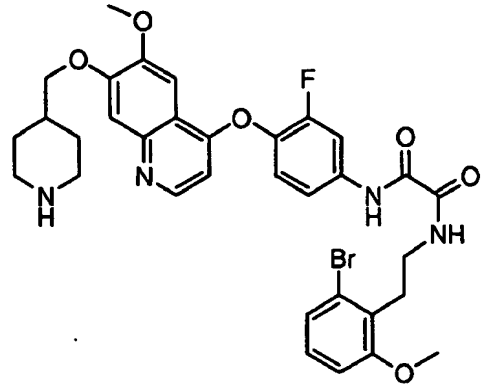
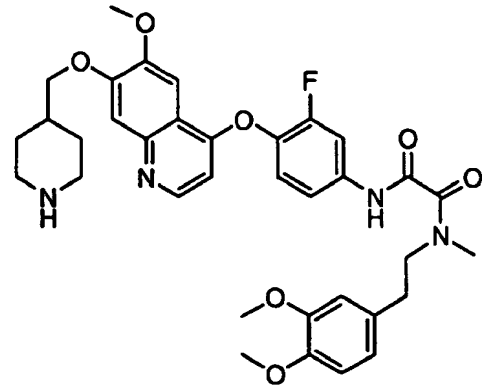
Entry	Name	Structure
278	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-fluoro-3-trifluoromethyl-benzyl)-oxalamide	
279	N-[2-(2-Bromo-6-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
280	N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N-methyl-oxalamide	

Table 1

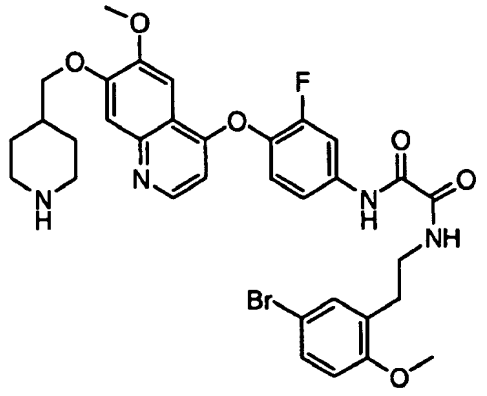
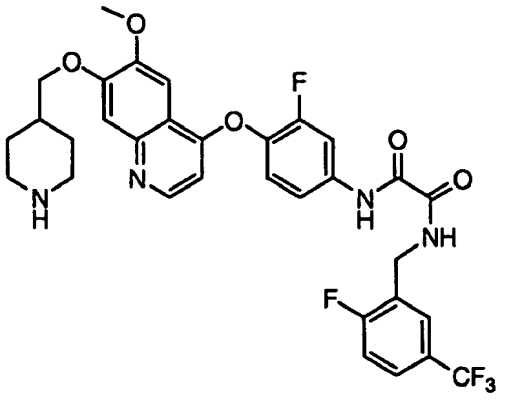
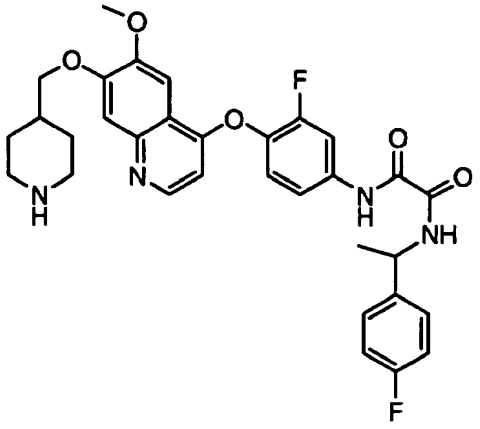
Entry	Name	Structure
281	N-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
282	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-fluoro-5-trifluoromethyl-benzyl)-oxalamide	
284	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[1-(4-fluoro-phenyl)-ethyl]-oxalamide	

Table 1

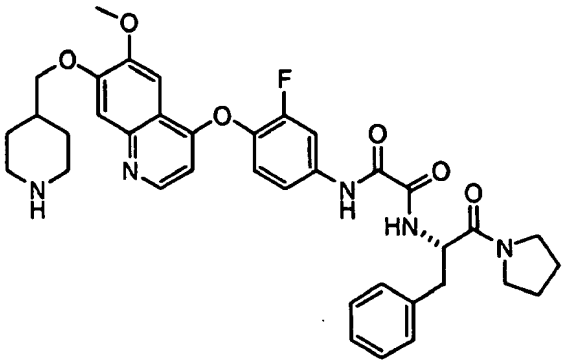
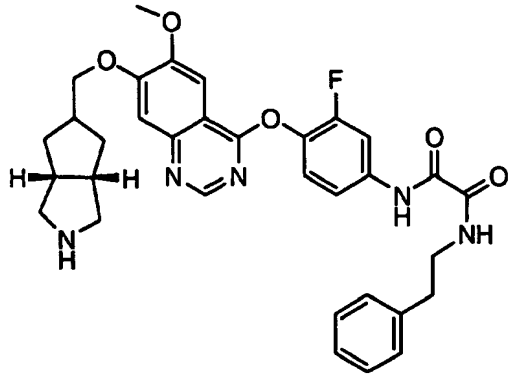
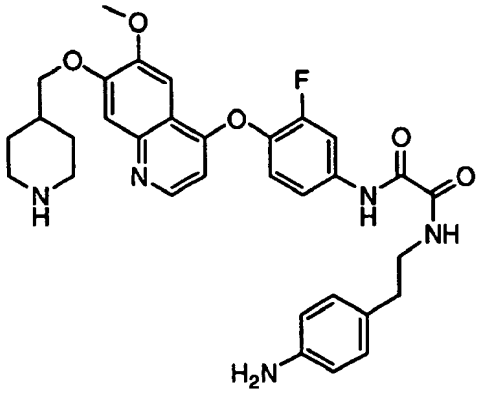
Entry	Name	Structure
285	N-(1S-Benzyl-2-oxo-2-pyrrolidin-1-yl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
286	N-{3-Fluoro-4-[6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
287	N-[2-(4-Amino-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 1

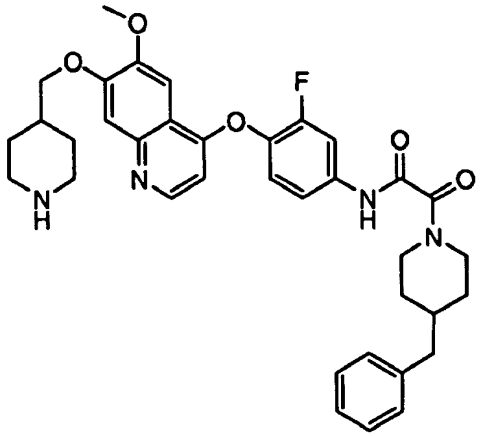
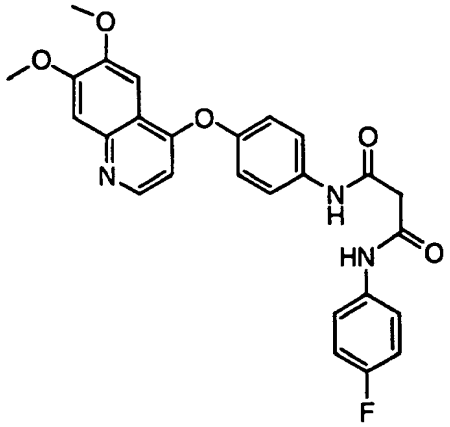
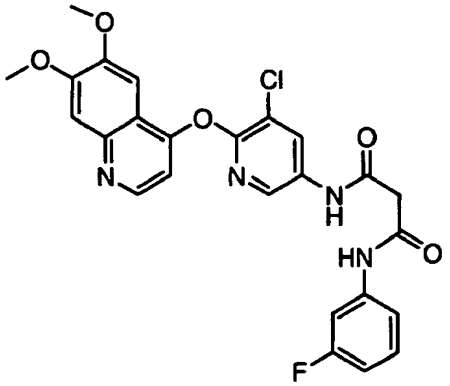
Entry	Name	Structure
288	2-(4-Benzyl-piperidin-1-yl)-N-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-acetamide	
289	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenyl]-N'-(4-fluoro-phenyl)-malonamide	
291	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(3-fluoro-phenyl)-malonamide	

Table 1

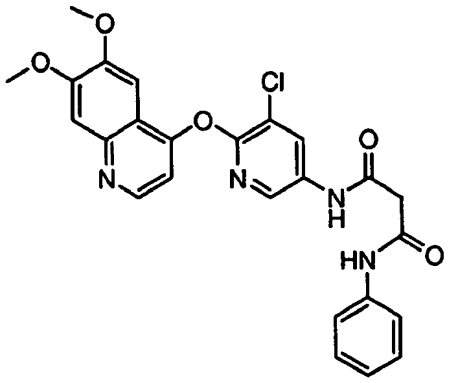
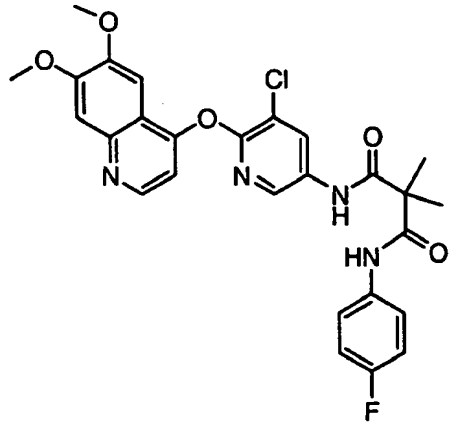
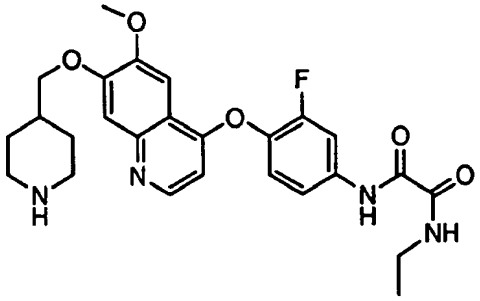
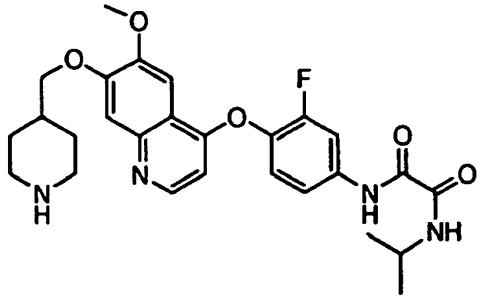
Entry	Name	Structure
292	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-phenyl-malonamide	
293	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(4-fluoro-phenyl)-2,2-dimethyl-malonamide	
294	N-Ethyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
295	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-isopropyl-oxalamide	

Table 1

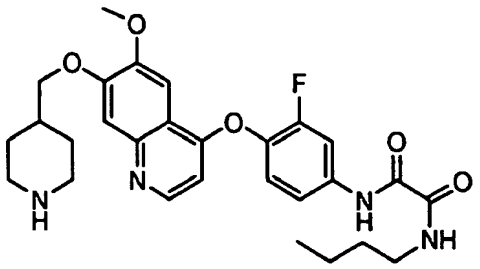
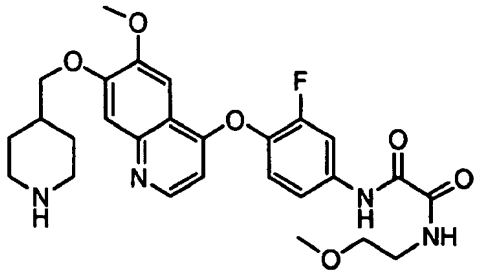
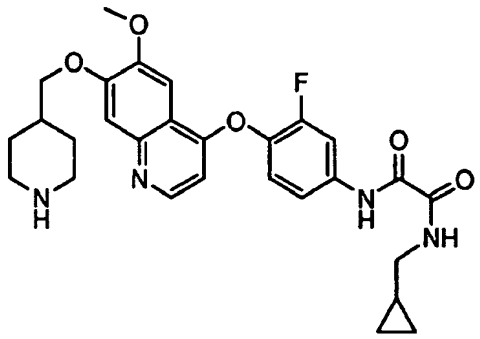
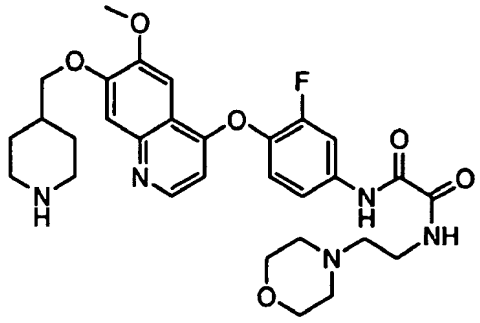
Entry	Name	Structure
296	N-Butyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
297	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-methoxy-ethyl)-oxalamide	
298	N-Cyclopropylmethyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
299	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-morpholin-4-yl-ethyl)-oxalamide	

Table 1

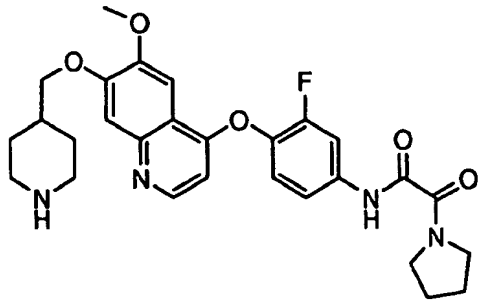
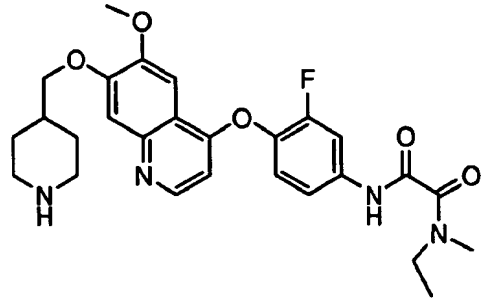
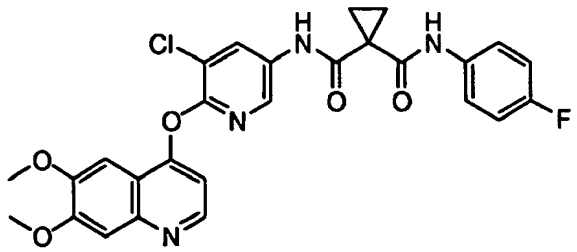
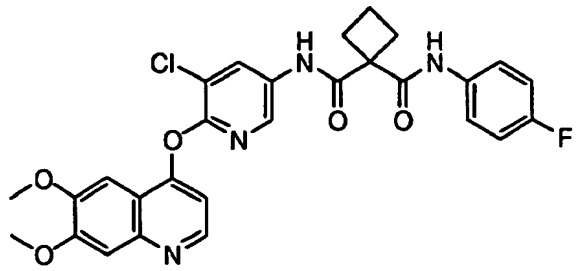
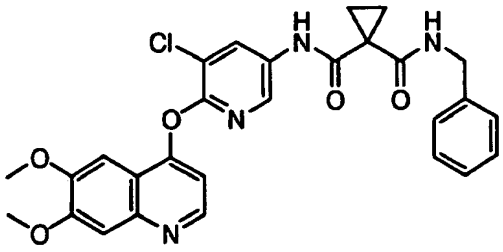
Entry	Name	Structure
300	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-pyrrolidin-1-yl-acetamide	
301	N-Ethyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N-methyl-oxalamide	
302	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
303	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
304	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(phenylmethyl)cyclopropane-1,1-dicarboxamide	

Table 1

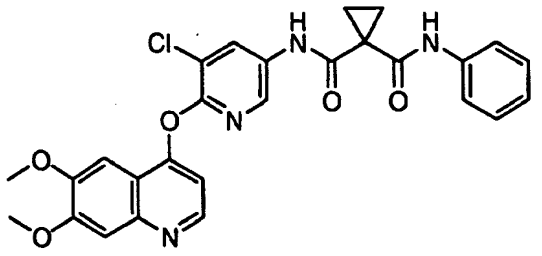
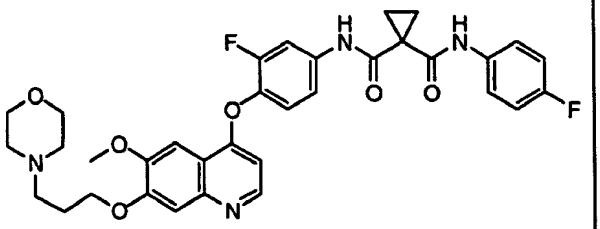
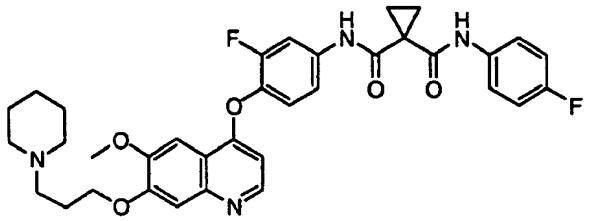
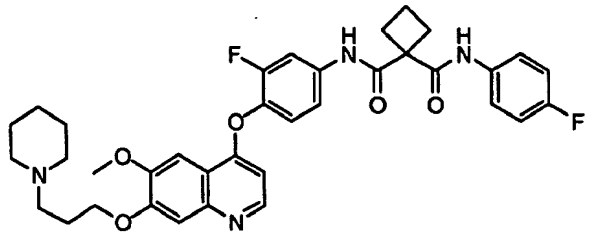
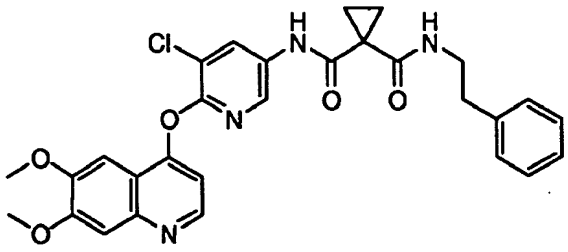
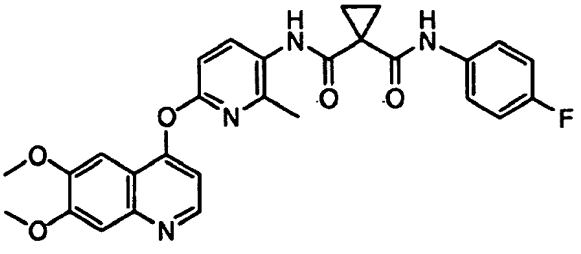
Entry	Name	Structure
305	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-phenylcyclopropane-1,1-dicarboxamide	
306	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
307	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
308	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
309	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl)cyclopropane-1,1-dicarboxamide	
310	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 1

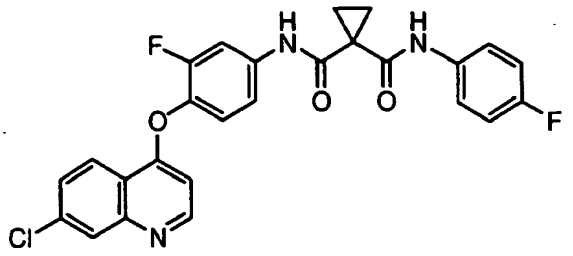
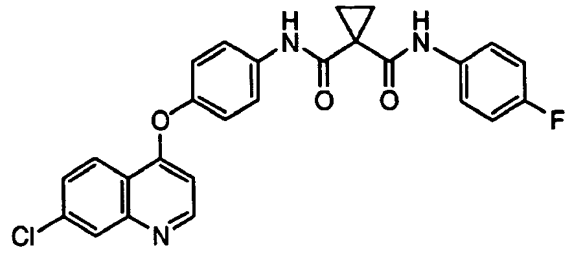
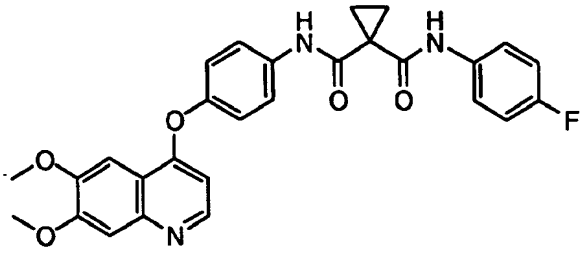
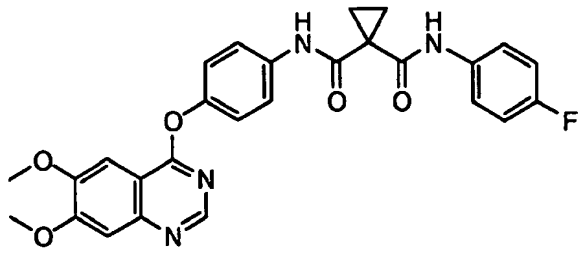
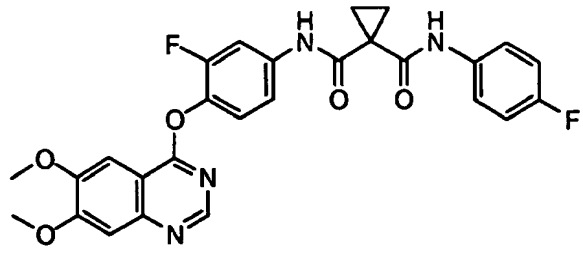
Entry	Name	Structure
311	N-{4-[(7-chloroquinolin-4-yl)oxy]-3-fluorophenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
312	N-{4-[(7-chloroquinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
313	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
314	N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
315	N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 1

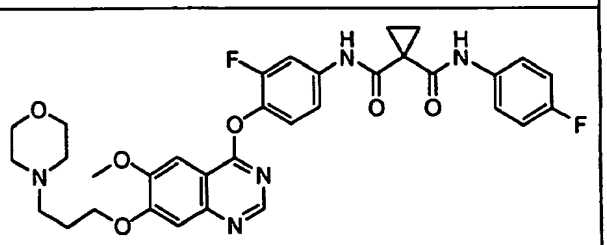
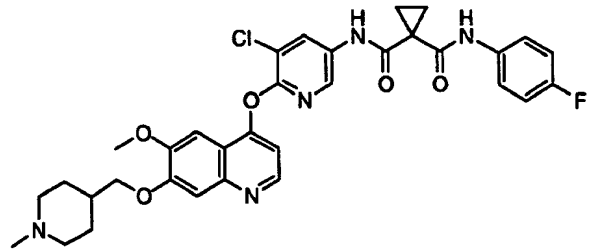
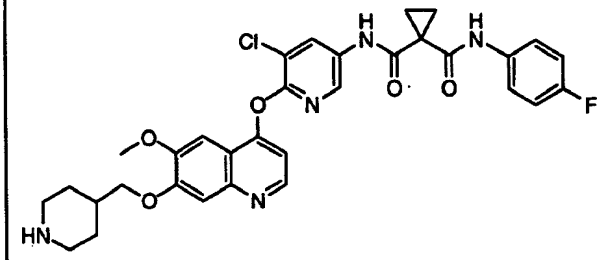
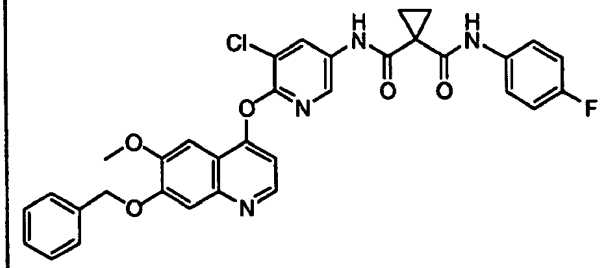
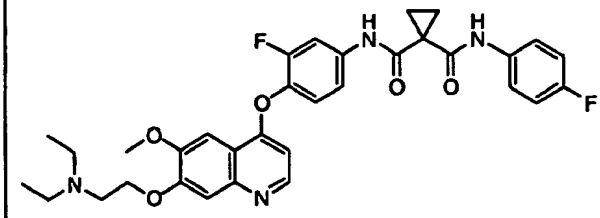
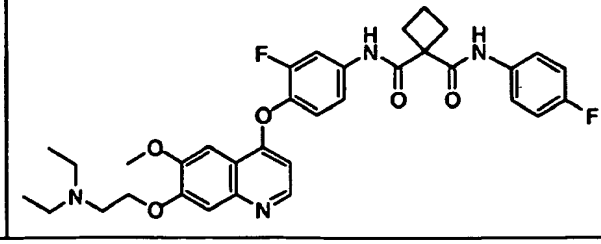
Entry	Name	Structure
316	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
317	N-{5-chloro-6-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]pyridin-3-yl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
318	N-[5-chloro-6-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
319	N-[5-chloro-6-({6-(methyloxy)-7-[(phenylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
320	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
321	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	

Table 1

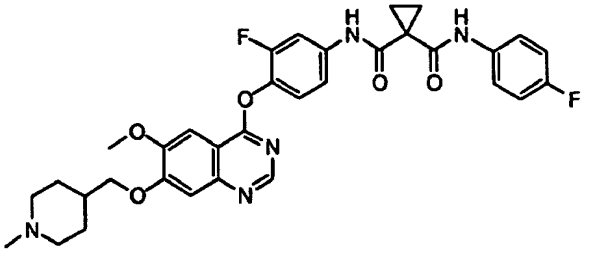
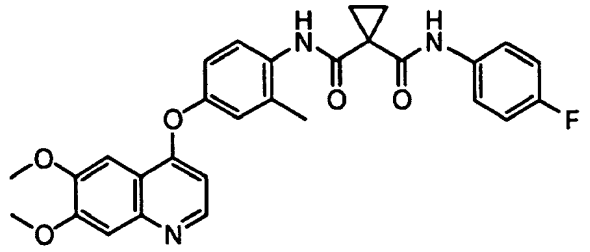
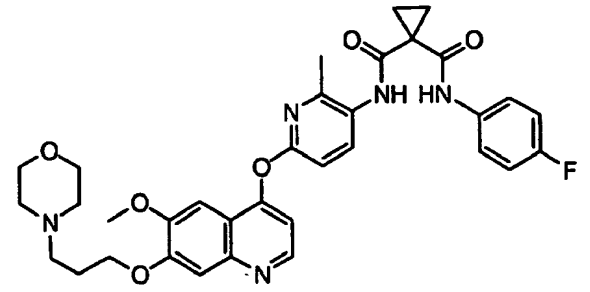
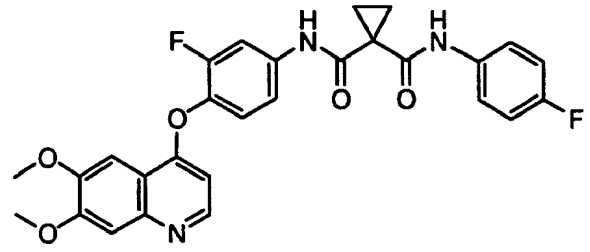
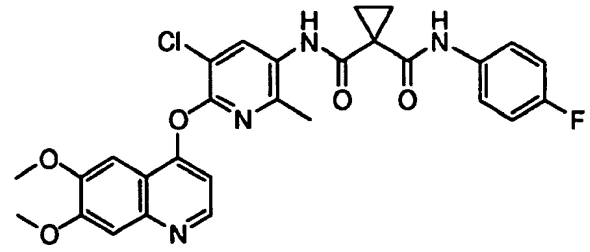
Entry	Name	Structure
322	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
323	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
324	N-(4-fluorophenyl)-N'-[2-methyl-6-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]cyclopropane-1,1-dicarboxamide	
325	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
326	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloro-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 1

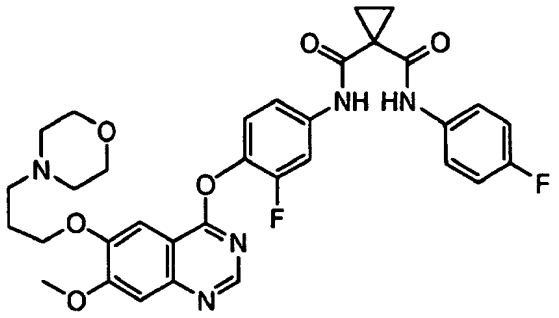
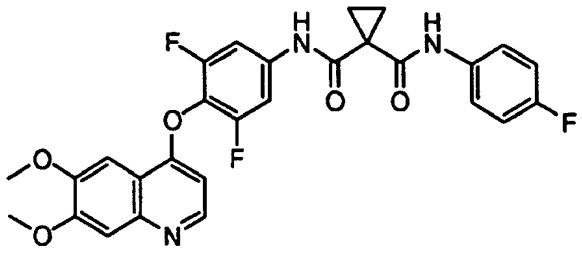
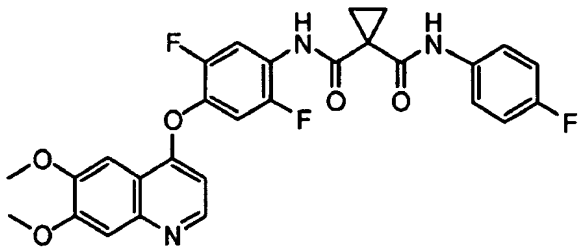
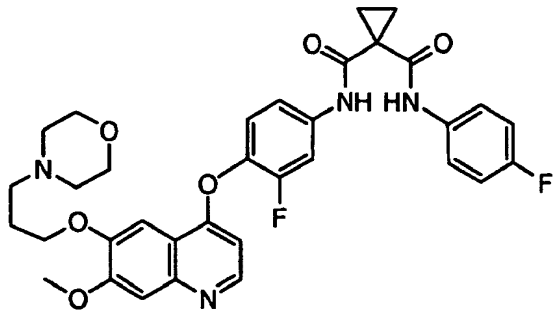
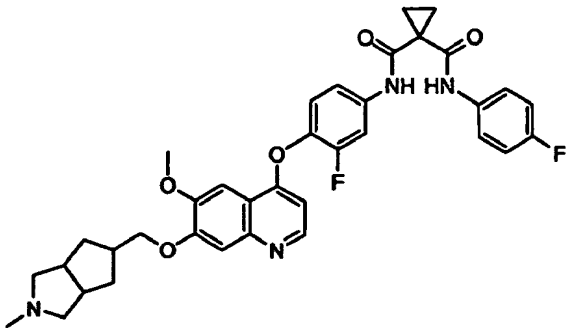
Entry	Name	Structure
327	N-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
328	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3,5-difluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
329	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,5-difluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
330	N-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
331	N-{3-fluoro-4-[(6-(methyloxy)-7-(2-methyl octahydrocyclopenta[c]pyrrol-5-ylmethoxy)quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 1

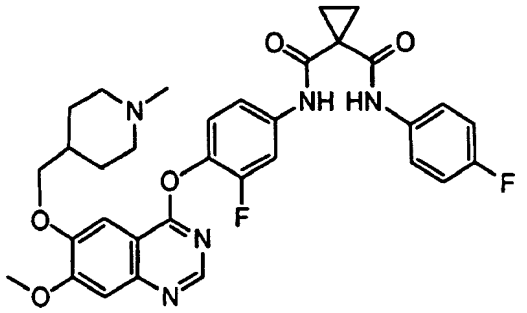
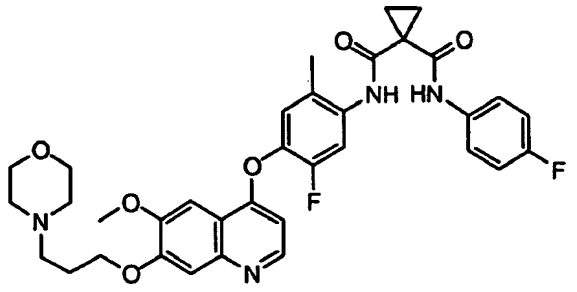
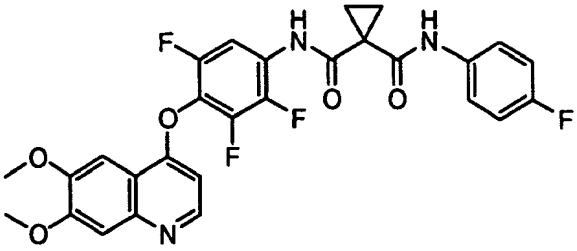
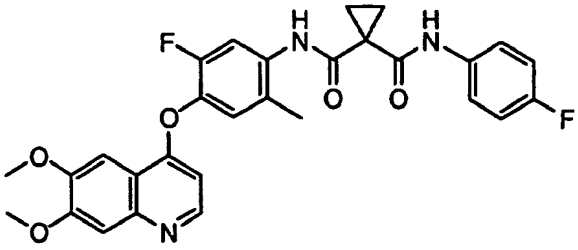
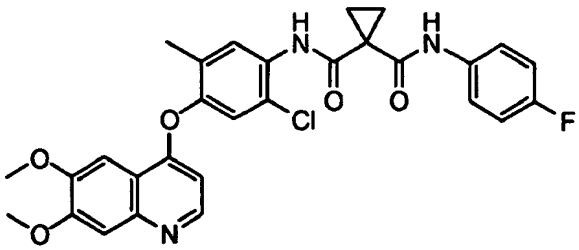
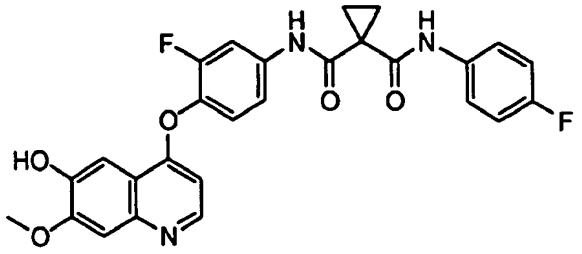
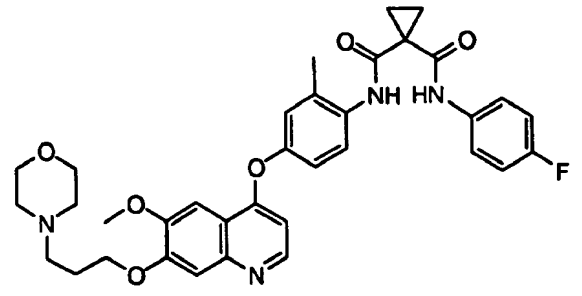
Entry	Name	Structure
332	N-{3-fluoro-4-[(7-(methyloxy)-6-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
333	N-[5-fluoro-2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
334	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,3,5-trifluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
335	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
336	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 1

Entry	Name	Structure
337	N-(3-fluoro-4-{[6-hydroxy-7-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
338	N-(4-fluorophenyl)-N'-[2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide	

[0066] In another example the process is according to any of paragraphs [0014] - [0065], further comprising converting said compound to a pharmaceutically acceptable salt, hydrate, or prodrug thereof.

Definitions

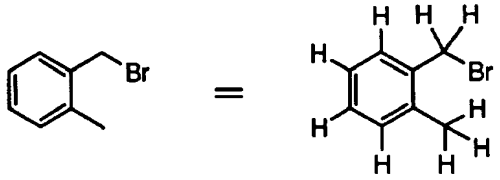
[0067] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise or they are expressly defined to mean something different.

[0068] The symbol "-" means a single bond, "=" means a double bond, "≡" means a triple bond. The symbol "〰" refers to a group on a double-bond as occupying either position on the terminus of a double bond to which the symbol is attached; that is, the geometry, *E*- or *Z*-, of the double bond is ambiguous. When a group is depicted removed from its parent formula, the "〜" symbol will be used at the end of the bond which was theoretically cleaved in order to separate the group from its parent structural formula.

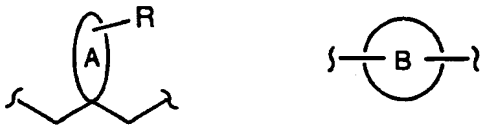
[0069] Chemical formulae use descriptors such as "R^1" accompanied by a list of formulae or verbage describing the scope of what is meant by the descriptor. A subsequent descriptor

such as "R^{1a}" is used to describe some subset of the scope of R^1, and "R^{1b}" is used to describe another subset of the scope of R^1, and so on. In such subsequent cases, all other formulae containing simply "R^1" are meant to include the entire scope of the descriptor.

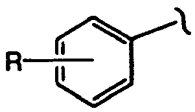
[0070] When chemical structures are depicted or described, unless explicitly stated otherwise, all carbons are assumed to have hydrogen substitution to conform to a valence of four. For example, in the structure on the left-hand side of the schematic below there are nine hydrogens implied. The nine hydrogens are depicted in the right-hand structure. Sometimes a particular atom in a structure is described in textual formula as having a hydrogen or hydrogens as substitution (expressly defined hydrogen), for example, $-CH_2CH_2-$. It is understood by one of ordinary skill in the art that the aforementioned descriptive techniques are common in the chemical arts to provide brevity and simplicity to description of otherwise complex structures.



[0071] In this application, some ring structures are depicted generically and will be described textually. For example, in the schematic below, if in the structure on the left, ring A is used to describe, for example a cyclopropyl, there are at most four hydrogens on ring A (when "R" can also be -H). In another example, as depicted on the right side of the schematic below, if ring B is used to describe a "phenylene" then there can be at most four hydrogens on ring B (assuming depicted cleaved bonds are not C-H bonds).

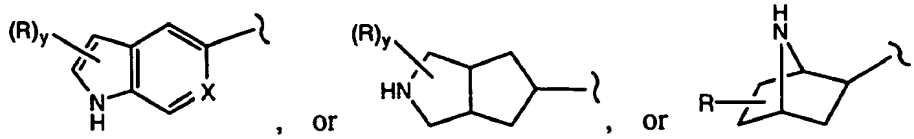


[0072] If a group "R" is depicted as "floating" on a ring system, as for example in the formula:



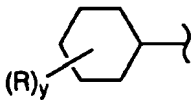
then, unless otherwise defined, a substituent "R" may reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

[0073] If a group "R" is depicted as floating on a fused ring system, as for example in the formulae:

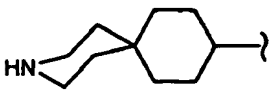


then, unless otherwise defined, a substituent "R" may reside on any atom of the fused ring system, assuming replacement of a depicted hydrogen (for example the -NH- in the formula above), implied hydrogen (for example as in the formula above, where the hydrogens are not shown but understood to be present), or expressly defined hydrogen (for example where in the formula above, "X" equals =CH-) from one of the ring atoms, so long as a stable structure is formed. In the example depicted, the "R" group may reside on either the 5-membered or the 6-membered ring of the fused ring system. In the formula depicted above, when y is 2 for example, then the two "R's" may reside on any two atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

[0074] When a group "R" is depicted as existing on a ring system containing saturated carbons, as for example in the formula:



where, in this example, "y" can be more than one, assuming each replaces a currently depicted, implied, or expressly defined hydrogen on the ring; then, unless otherwise defined, where the resulting structure is stable, two "R's" may reside on the same carbon. A simple example is when R is a methyl group; there can exist a geminal dimethyl on a carbon of the depicted ring (an "annular" carbon). In another example, two R's on the same carbon, including that carbon, may form a ring, thus creating a spirocyclic ring (a "spirocyclyl" group) structure with the depicted ring as for example in the formula:



[0075] "Alkyl" is intended to include linear, branched, or cyclic hydrocarbon structures and combinations thereof, inclusively. For example, "C_8 alkyl" may refer to an *n*-octyl, *iso*-octyl, cyclohexylethyl, and the like. Lower alkyl refers to alkyl groups of from one to six carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *s*-butyl, *t*-butyl, isobutyl, pentyl, hexyl and the like. Higher alkyl refers to alkyl groups containing more that eight carbon atoms. Exemplary alkyl groups are those of C_{20} or below. Cycloalkyl is a subset of alkyl and includes cyclic hydrocarbon groups of from three to thirteen carbon atoms. Examples of cycloalkyl groups include c-propyl, c-butyl, c-pentyl, norbornyl, adamantyl and the like. In this application, alkyl refers to alkanyl, alkenyl, and alkynyl residues (and combinations thereof); it is intended to include cyclohexylmethyl, vinyl, allyl, isoprenyl, and the like. Thus, when an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of *carbons* are intended to be encompassed; thus, for example, either "butyl" or "C_4alkyl" is meant to include *n*-butyl, *sec*-butyl, isobutyl, *t*-butyl, isobutenyl and but-2-yne radicals; and for example, "propyl" or "C_3alkyl" each include *n*-propyl, propenyl, and isopropyl. Otherwise, if alkenyl and/or alkynyl descriptors *are used* in a particular definition of a group, for example "C_4alkyl" along "C_4alkenyl," then C_4alkenyl geometric isomers are not meant to be included in "C_4alkyl," but other 4-carbon isomers are, for example C_4alkynyl. For example, a more general description, intending to encompass the invention as a whole may describe a particular group as "$C_{1\text{-}8}$alkyl" while a preferred species may describe the same group as including, "$C_{1\text{-}8}$alkyl," "$C_{1\text{-}6}$alkenyl" and "$C_{1\text{-}5}$alkynyl."

[0076] "Alkylene" refers to straight or branched chain divalent radical consisting solely of carbon and hydrogen atoms, containing no unsaturation and having from one to ten carbon atoms, for example, methylene, ethylene, propylene, *n*-butylene and the like. Alkylene is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, fully saturated. Examples of alkylene include ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$), dimethylpropylene ($-CH_2C(CH_3)_2CH_2-$), and cyclohexylpropylene ($-CH_2CH_2CH(C_6H_{13})$).

[0077] "Alkylidene" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms, having from two to ten carbon atoms, for example, ethylidene, propylidene, *n*-butylidene, and the like. Alkylidene is a subset of alkyl,

referring to the same residues as alkyl, but having two points of attachment and, specifically, double bond unsaturation. The unsaturation present includes at least one double bond.

[0078] "Alkylidyne" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms having from two to ten carbon atoms, for example, propylid-2-ynyl, *n*-butylid-1-ynyl, and the like. Alkylidyne is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, triple bond unsaturation. The unsaturation present includes at least one triple bond.

[0079] Any of the above radicals, "alkylene," "alkylidene" and "alkylidyne," when optionally substituted, may contain alkyl substitution which itself contains unsaturation. For example, 2-(2-phenylethynyl-but-3-enyl)-naphthalene (IUPAC name) contains an *n*-butylid-3-ynyl radical with a vinyl substituent at the 2-position of said radical.

[0080] "Alkoxy" or "alkoxyl" refers to the group -O-alkyl, for example including from one to eight carbon atoms of a straight, branched, cyclic configuration, unsaturated chains, and combinations thereof attached to the parent structure through an oxygen atom. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like. Lower-alkoxy refers to groups containing one to six carbons.

[0081] "Substituted alkoxy" refers to the group -O-(substituted alkyl), the substitution on the alkyl group generally containing more than only carbon (as defined by alkoxy). One exemplary substituted alkoxy group is "polyalkoxy" or -O-optionally substituted alkylene-optionally substituted alkoxy, and includes groups such as $-OCH_2CH_2OCH_3$, and glycol ethers such as polyethyleneglycol and $-O(CH_2CH_2O)_xCH_3$, where x is an integer of between about two and about twenty, in another example, between about two and about ten, and in a further example between about two and about five. Another exemplary substituted alkoxy group is hydroxyalkoxy or $-OCH_2(CH_2)_yOH$, where y is for example an integer of between about one and about ten, in another example y is an integer of between about one and about four.

[0082] "Acyl" refers to groups of from one to ten carbon atoms of a straight, branched, cyclic configuration, saturated, unsaturated and aromatic and combinations thereof, attached to the parent structure through a carbonyl functionality. One or more carbons in the acyl residue may be replaced by nitrogen, oxygen or sulfur as long as the point of attachment to the parent remains at the carbonyl. Examples include acetyl, benzoyl, propionyl, isobutyryl, *t*-

butoxycarbonyl, benzyloxycarbonyl and the like. Lower-acyl refers to groups containing one to six carbons.

[0083] "α-Amino Acids" refer to naturally occurring and commercially available amino acids and optical isomers thereof. Typical natural and commercially available α-amino acids are glycine, alanine, serine, homoserine, threonine, valine, norvaline, leucine, isoleucine, norleucine, aspartic acid, glutamic acid, lysine, omithine, histidine, arginine, cysteine, homocysteine, methionine, phenylalanine, homophenylalanine, phenylglycine, ortho-tyrosine, meta-tyrosine, para-tyrosine, tryptophan, glutamine, asparagine, proline and hydroxyproline. A "side chain of an α-amino acid" refers to the radical found on the α-carbon of an α-amino acid as defined above, for example, hydrogen (for glycine), methyl (for alanine), benzyl (for phenylalanine), and the like.

[0084] "Amino" refers to the group $-NH_2$. "Substituted amino," refers to the group -N(H)R or –N(R)R where each R is independently selected from the group: optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted heterocyclyl, acyl, carboxy, alkoxycarbonyl, sulfanyl, sulfinyl and sulfonyl, for example, diethylamino, methylsulfonylamino, and furanyl-oxy-sulfonamino.

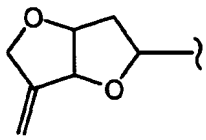
[0085] "Aryl" refers to aromatic six- to fourteen-membered carbocyclic ring, for example, benzene, naphthalene, indane, tetralin, fluorene and the like, univalent radicals. As univalent radicals, the aforementioned ring examples are named, phenyl, naphthyl, indanyl, tetralinyl, and fluorenyl.

[0086] "Arylene" generically refers to any aryl that has at least two non-hydrogen groups attached thereto. For a more specific example, "phenylene" refers to a divalent phenyl ring radical. A phenylene, thus may have more than two groups attached, but is defined by a minimum of two non-hydrogen groups attached thereto. The terms "ortho-arylene," "meta-arylene" or "para-arylene" refer to geometrical isomers of a particular arylene wherein, two groups attached to an aryl as depicted in a formula are situated in an ortho, meta or para geometrical relationship about the aryl, respectively.

[0087] "Arylalkyl" refers to a residue in which an aryl moiety is attached to a parent structure via one of an alkylene, alkylidene, or alkylidyne radical. Examples include benzyl, phenethyl, phenylvinyl, phenylallyl and the like. Both the aryl, and the corresponding alkylene, alkylidene, or alkylidyne radical portion of an arylalkyl group may be optionally

substituted. "Lower arylalkyl" refers to an arylalkyl where the "alkyl" portion of the group has one to six carbons; this can also be refered to as aryl $C_{1\text{-}6}$alkyl.

[0088] "Exo-alkenyl" refers to a double bond that emanates from an annular carbon, and is not within the ring system, for example the double bond depicted in the formula below.



[0089] In some examples, as appreciated by one of ordinary skill in the art, two adjacent groups on an aromatic system may be fused together to form a ring structure. The fused ring structure may contain heteroatoms and may be optionally substituted with one or more groups. It should additionally be noted that saturated carbons of such fused groups (i.e. saturated ring structures) can contain two substitution groups.

[0090] "Fused-polycyclic" or "fused ring system" refers to a polycyclic ring system that contains bridged or fused rings; that is, where two rings have more than one shared atom in their ring structures. In this application, fused-polycyclics and fused ring systems are not necessarily all aromatic ring systems. Typically, but not necessarily, fused-polycyclics share a vicinal set of atoms, for example naphthalene or 1,2,3,4-tetrahydro-naphthalene. A spiro ring system is not a fused-polycyclic by this definition, but fused polycyclic ring systems of the invention may themselves have spiro rings attached thereto via a single ring atom of the fused-polycyclic.

[0091] "Halogen" or "halo" refers to fluorine, chlorine, bromine or iodine. "Haloalkyl" and "haloaryl" refer generically to alkyl and aryl radicals that are substituted with one or more halogens, respectively. Thus, "dihaloaryl," "dihaloalkyl," "trihaloaryl" etc. refer to aryl and alkyl substituted with a plurality of halogens, but not necessarily a plurality of the same halogen; thus 4-chloro-3-fluorophenyl is within the scope of dihaloaryl.

[0092] "Heteroarylene" generically refers to any heteroaryl that has at least two groups attached thereto. For a more specific example, "pyridylene" refers to a divalent pyridyl ring radical. A pyridylene, thus may have more than two groups attached, but is defined by a minimum of two non-hydrogen groups attached thereto. For the purposes of this application, the term "ortho-heteroarylene" refers to a geometrical isomer of a particular heteroarylene

wherein two groups attached to a heteroaryl as depicted in a formula are situated on contiguous atoms of the heteroaryl.

[0093] "Heteroatom" refers to O, S, N, or P.

[0094] "Heterocyclyl" refers to a stable three- to fifteen-membered ring radical that consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclyl radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused or bridged ring systems as well as spirocyclic systems; and the nitrogen, phosphorus, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized to various oxidation states. In a specific example, the group $-S(O)_{0-2}-$, refers to -S- (sulfide), -S(O)- (sulfoxide), and $-SO_2-$ (sulfone). For convenience, nitrogens, particularly but not exclusively, those defined as annular aromatic nitrogens, are meant to include their corresponding *N*-oxide form, although not explicitly defined as such in a particular example. Thus, for a compound of the invention having, for example, a pyridyl ring; the corresponding pyridyl-*N*-oxide is meant to be included as another compound of the invention. In addition, annular nitrogen atoms may be optionally quaternized; and the ring radical may be partially or fully saturated or aromatic. Examples of heterocyclyl radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofuranyl, carbazoyl, cinnolinyl, dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl, tetrahydroisoquinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, dihydropyridinyl, tetrahydropyridinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxazolidinyl, triazolyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothieliyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, dioxaphospholanyl, and oxadiazolyl.

[0095] "Heteroalicyclic" refers specifically to a non-aromatic heterocyclyl radical. A heteroalicyclic may contain unsaturation, but is not aromatic.

[0096] "Heteroaryl" refers specifically to an aromatic heterocyclyl radical.

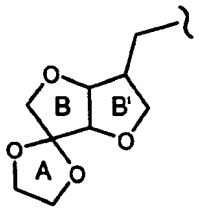
[0097] "Heterocyclylalkyl" refers to a residue in which a heterocyclyl is attached to a parent structure via one of an alkylene, alkylidene, or alkylidyne radical. Examples include (4-methylpiperazin-1-yl) methyl, (morpholin-4-yl) methyl, (pyridine-4-yl) methyl, 2-(oxazolin-2-yl) ethyl, 4-(4-methylpiperazin-1-yl)-2-butenyl, and the like. Both the heterocyclyl, and the corresponding alkylene, alkylidene, or alkylidyne radical portion of a heterocyclylalkyl group may be optionally substituted. "Lower heterocyclylalkyl" refers to a heterocyclylalkyl where the "alkyl" portion of the group has one to six carbons. "Heteroalicyclylalkyl" refers specifically to a heterocyclylalkyl where the heterocyclyl portion of the group is non-aromatic; and "heteroarylalkyl" refers specifically to a heterocyclylalkyl where the heterocyclyl portion of the group is aromatic Such terms may be described in more than one way, for example, "lower heterocyclylalkyl" and "heterocyclyl C_{1-6}alkyl" are equivalent terms.

[0098] "Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. One of ordinary skill in the art would understand that, with respect to any molecule described as containing one or more optional substituents, that only sterically practical and/or synthetically feasible compounds are meant to be included. "Optionally substituted" refers to all subsequent modifiers in a term, for example in the term "optionally substituted aryl C_{1-8}alkyl," optional substitution may occur on both the "C_{1-8}alkyl" portion and the "aryl" portion of the molecule; and for example, optionally substituted alkyl includes optionally substituted cycloalkyl groups, which in turn are defined as including optionally substituted alkyl groups, potentially *ad infinitum*. A list of exemplary optional substitutions is included below in the definition of "substituted."

[0099] "Saturated bridged ring system" refers to a bicyclic or polycyclic ring system that is not aromatic. Such a system may contain isolated or conjugated unsaturation, but not aromatic or heteroaromatic rings in its core structure (but may have aromatic substitution thereon). For example, hexahydro-furo[3,2-b]furan, 2,3,3a,4,7,7a-hexahydro-1H-indene, 7-

aza-bicyclo[2.2.1]heptane, and 1,2,3,4,4a,5,8,8a-octahydro-naphthalene are all included in the class "saturated bridged ring system.

[0100] "Spirocyclyl" or "spirocyclic ring" refers to a ring originating from a particular annular carbon of another ring. For example, as depicted below, a ring atom of a saturated bridged ring system (rings B and B'), but not a bridgehead atom, can be a shared atom between the saturated bridged ring system and a spirocyclyl (ring A) attached thereto. A spirocyclyl can be carbocyclic or heteroalicyclic.



[0101] "Substituted" alkyl, aryl, and heterocyclyl, refer respectively to alkyl, aryl, and heterocyclyl, wherein one or more (for example up to about five, in another example, up to about three) hydrogen atoms are replaced by a substituent independently selected from: optionally substituted alkyl (for example, fluoromethyl, hydroxypropyl, nitromethyl, aminoethyl and the like.), optionally substituted aryl (for example, 4-hydroxyphenyl, 2,3-difluorophenyl, and the like), optionally substituted arylalkyl (for example, 1-phenyl-ethyl, *para*-methoxyphenylethyl and the like), optionally substituted heterocyclylalkyl (for example, 1-pyridin-3-yl-ethyl, N-ethylmorphonlino and the like), optionally substituted heterocyclyl (for example, 5-chloro-pyridin-3-yl, 1-methyl-piperidin-4-yl and the like), optionally substituted alkoxy (for example methoxyethoxy, hydroxypropyloxy, methylenedioxy and the like), optionally substituted amino (for example, methylamino, diethylamino, trifluoroacetylamino and the like), optionally substituted amidino, optionally substituted aryloxy (for example, phenoxy, *para*-chlorophenoxy, *meta*-aminophenoxy, *para*-phenoxyphenoxy and the like), optionally substituted arylalkyloxy (for example, benzyloxy, 3-chlorobenzyloxy, *meta*-phenoxybenzyloxy and the like), carboxy (-CO_2H), optionally substituted carboalkoxy (that is, acyloxy or -OC(=O)R), optionally substituted carboxyalkyl (that is, esters or -CO_2R), optionally substituted carboxamido, optionally substituted benzyloxycarbonylamino (CBZ-amino), cyano, optionally substituted acyl, halogen, hydroxy, nitro, optionally substituted alkylsulfanyl, optionally substituted alkylsulfinyl, optionally substituted alkylsulfonyl, thiol, oxo, carbamyl, optionally substituted acylamino,

optionally substituted hydrazino, optionally substituted hydroxylamino, and optionally substituted sulfonamido.

[0102] "Suitable leaving group" is defined as the term would be understood by one of ordinary skill in the art; that is, a carbon with such a group attached, upon reaction wherein a new bond is to be formed, loses such a group upon formation of the new bond. The invention pertains particularly with respect convergent synthesis, to reactions where such a leaving group is bonded to a reaction partner that is aromatic, undergoes a bond-forming reaction and remains aromatic. A typical example of such a reaction is a nucleophilic aromatic substitution reaction, as would be understood by one of ordinary skill in the art. However, the invention is not limited to such mechanistic restrictions; for example, reactions where there is, for example, an insertion reaction (for example by a transition metal) into the bond between the aromatic reaction partner and its leaving group followed by reductive coupling can also be used within the scope of the invention. Examples of suitable leaving groups include halogens, optionally substituted aryl or alkyl sulfonates, phosphonates, azides, $RS(O)_{0-2}$- where R is, for example optionally substituted alkyl, optionally substituted aryl, or optionally substituted heteroaryl.

[0103] "Sulfanyl" refers to the groups: -S-(optionally substituted alkyl), -S-(optionally substituted aryl), and -S-(optionally substituted heterocyclyl).

[0104] "Sulfinyl" refers to the groups: -S(O)-H, -S(O)-(optionally substituted alkyl), -S(O)-optionally substituted aryl), and -S(O)-(optionally substituted heterocyclyl).

[0105] "Sulfonyl" refers to the groups: $-S(O_2)$-H, $-S(O_2)$-(optionally substituted alkyl), $-S(O_2)$-optionally substituted aryl), $-S(O_2)$-(optionally substituted heterocyclyl), $-S(O_2)$-(optionally substituted alkoxy), $-S(O_2)$-optionally substituted aryloxy), and $-S(O_2)$-(optionally substituted heterocyclyloxy).

[0106] "Yield" for each of the reactions described herein is expressed as a percentage of the theoretical yield.

[0107] Some of the compounds of the invention may have imino, amino, oxo or hydroxy substituents off aromatic heterocyclyl systems. For purposes of this disclosure, it is understood that such imino, amino, oxo or hydroxy substituents may exist in their corresponding tautomeric form, i.e., amino, imino, hydroxy or oxo, respectively.

[0108] Compounds of the invention are named according to systematic application of the nomenclature rules agreed upon by the International Union of Pure and Applied Chemistry (IUPAC), International Union of Biochemistry and Molecular Biology (IUBMB), and the Chemical Abstracts Service (CAS).

[0109] The compounds of the invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms, oxidized sulfur atoms or quaternized nitrogen atoms in their structure.

[0110] The compounds of the invention and their pharmaceutically acceptable salts may exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. The compounds may also exist as geometric isomers. All such single stereoisomers, racemates and mixtures thereof, and geometric isomers are intended to be within the scope of this invention.

[0111] It is assumed that when considering generic descriptions of compounds of the invention for the purpose of constructing a compound, such construction results in the creation of a stable structure. That is, one of ordinary skill in the art would recognize that there can theoretically be some constructs which would not normally be considered as stable compounds (that is, sterically practical and/or synthetically feasible, *supra*).

[0112] When a particular group with its bonding structure is denoted as being bonded to two partners; that is, a divalent radical, for example, -OCH_2-, then it is understood that either of the two partners may be bound to the particular group at one end, and the other partner is necessarily bound to the other end of the particular group, unless stated explicitly otherwise. Stated another way, divalent radicals are not to be construed as limited to the depicted orientation, for example "-OCH_2-" is meant to mean not only "-OCH_2-" as drawn, but also "-CH_2O-."

[0113] Methods for the preparation and/or separation and isolation of single stereoisomers from racemic mixtures or non-racemic mixtures of stereoisomers are well known in the art. For example, optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. Enantiomers (R- and S-isomers) may be resolved by methods known to one of ordinary skill in the art, for example by: formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which may be separated, for

example, by crystallization, selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where a desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step may be required to liberate the desired enantiomeric form. Alternatively, specific enantiomer may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting on enantiomer to the other by asymmetric transformation. For a mixture of enantiomers, enriched in a particular enantiomer, the major component enantiomer may be further enriched (with concomitant loss in yield) by recrystallization.

[0114] "Patient" for the purposes of the present invention includes humans and other animals, particularly mammals, and other organisms. Thus the methods are applicable to both human therapy and veterinary applications. In a preferred embodiment the patient is a mammal, and in a most preferred embodiment the patient is human.

[0115] "Kinase-dependent diseases or conditions" refer to pathologic conditions that depend on the activity of one or more protein kinases. Kinases either directly or indirectly participate in the signal transduction pathways of a variety of cellular activities including proliferation, adhesion, migration, differentiation and invasion. Diseases associated with kinase activities include tumor growth, the pathologic neovascularization that supports solid tumor growth, and associated with other diseases where excessive local vascularization is involved such as ocular diseases (diabetic retinopathy, age-related macular degeneration, and the like) and inflammation (psoriasis, rheumatoid arthritis, and the like).

[0116] While not wishing to be bound to theory, phosphatases can also play a role in "kinase-dependent diseases or conditions" as cognates of kinases; that is, kinases phosphorylate and phosphatases dephosphorylate, for example protein substrates. Therefore compounds of the invention, while modulating kinase activity as described herein, may also modulate, either directly or indirectly, phosphatase activity. This additional modulation, if present, may be synergistic (or not) to activity of compounds of the invention toward a related or otherwise interdependent kinase or kinase family. In any case, as stated previously, the compounds of

the invention are useful for treating diseases characterized in part by abnormal levels of cell proliferation (i.e. tumor growth), programmed cell death (apoptosis), cell migration and invasion and angiogenesis associated with tumor growth.

[0117] "Therapeutically effective amount" is an amount of a compound of the invention, that when administered to a patient, ameliorates a symptom of the disease. The amount of a compound of the invention which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease state and its severity, the age of the patient to be treated, and the like. The therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

[0118] "Cancer" refers to cellular-proliferative disease states, including but not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hanlartoma, inesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [neplrroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformians), meninges

(meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, SertoliLeydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma], fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal lands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

[0119] "Pharmaceutically acceptable acid addition salt" refers to those salts that retain the biological effectiveness of the free bases and that are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

[0120] "Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Exemplary salts are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine,

trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins, and the like. Exemplary organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine. (See, for example, S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19 which is incorporated herein by reference.)

[0121] "Prodrug" refers to compounds that are transformed (typically rapidly) *in vivo* to yield the parent compound of the above formulae, for example, by hydrolysis in blood. Common examples include, but are not limited to, ester and amide forms of a compound having an active form bearing a carboxylic acid moiety. Examples of pharmaceutically acceptable esters of the compounds of this invention include, but are not limited to, alkyl esters (for example with between about one and about six carbons) wherein the alkyl group is a straight or branched chain. Acceptable esters also include cycloalkyl esters and arylalkyl esters such as, but not limited to benzyl. Examples of pharmaceutically acceptable amides of the compounds of this invention include, but are not limited to, primary amides, and secondary and tertiary alkyl amides (for example with between about one and about six carbons). Amides and esters of the compounds of the present invention may be prepared according to conventional methods. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference for all purposes.

[0122] "Metabolite" refers to the break-down or end product of a compound or its salt produced by metabolism or biotransformation in the animal or human body; for example, biotransformation to a more polar molecule such as by oxidation, reduction, or hydrolysis, or to a conjugate (see Goodman and Gilman, "The Pharmacological Basis of Therapeutics" 8.sup.th Ed., Pergamon Press, Gilman et al. (eds), 1990 for a discussion of biotransformation). As used herein, the metabolite of a compound of the invention or its salt may be the biologically active form of the compound in the body. In one example, a prodrug may be used such that the biologically active form, a metabolite, is released *in vivo*. In

another example, a biologically active metabolite is discovered serendipitously, that is, no prodrug design *per se* was undertaken. An assay for activity of a metabolite of a compound of the present invention is known to one of skill in the art in light of the present disclosure.

[0123] In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

[0124] In addition, it is intended that the present invention cover compounds made either using standard organic synthetic techniques, including combinatorial chemistry or by biological methods, such as bacterial digestion, metabolism, enzymatic conversion, and the like.

[0125] "Treating" or "treatment" as used herein covers the treatment of a disease-state in a human, which disease-state is characterized by abnormal cellular proliferation, and invasion and includes at least one of: (i) preventing the disease-state from occurring in a human, in particular, when such human is predisposed to the disease-state but has not yet been diagnosed as having it; (ii) inhibiting the disease-state, i.e., arresting its development; and (iii) relieving the disease-state, i.e., causing regression of the disease-state. As is known in the art, adjustments for systemic versus localized delivery, age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition may be necessary, and will be ascertainable with routine experimentation by one of ordinary skill in the art.

[0126] One of ordinary skill in the art would understand that certain crystallized, protein-ligand complexes, in particular c-Met, c-Kit, KDR, flt-3, or flt-4-ligand complexes, and their corresponding x-ray structure coordinates can be used to reveal new structural information useful for understanding the biological activity of kinases as described herein. As well, the key structural features of the aforementioned proteins, particularly, the shape of the ligand binding site, are useful in methods for designing or identifying selective modulators of kinases and in solving the structures of other proteins with similar features. Such protein-ligand complexes, having compounds of the invention as their ligand component, are an aspect of the invention.

[0127] As well, one of ordinary skill in the art would appreciate that such suitable x-ray quality crystals can be used as part of a method of identifying a candidate agent capable of binding to and modulating the activity of kinases. Such methods may be characterized by the following aspects: a) introducing into a suitable computer program, information defining a ligand binding domain of a kinase in a conformation (e.g. as defined by x-ray structure coordinates obtained from suitable x-ray quality crystals as described above) wherein the computer program creates a model of the three dimensional structures of the ligand binding domain, b) introducing a model of the three dimensional structure of a candidate agent in the computer program, c) superimposing the model of the candidate agent on the model of the ligand binding domain, and d) assessing whether the candidate agent model fits spatially into the ligand binding domain. Aspects a-d are not necessarily carried out in the aforementioned order. Such methods may further entail: performing rational drug design with the model of the three-dimensional structure, and selecting a potential candidate agent in conjunction with computer modeling.

[0128] Additionally, one of ordinary skill in the art would appreciate that such methods may further entail: employing a candidate agent, so-determined to fit spatially into the ligand binding domain, in a biological activity assay for kinase modulation, and determining whether said candidate agent modulates kinase activity in the assay. Such methods may also include administering the candidate agent, determined to modulate kinase activity, to a mammal suffering from a condition treatable by kinase modulation, such as those described above.

[0129] Also, one of ordinary skill in the art would appreciate that compounds of the invention can be used in a method of evaluating the ability of a test agent to associate with a molecule or molecular complex comprising a ligand binding domain of a kinase. Such a method may be characterized by the following aspects: a) creating a computer model of a kinase binding pocket using structure coordinates obtained from suitable x-ray quality crystals of the kinase, b) employing computational algorithms to perform a fitting operation between the test agent and the computer model of the binding pocket, and c) analyzing the results of the fitting operation to quantify the association between the test agent and the computer model of the binding pocket.

General Administration

[0130] Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, intracistemally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages.

[0131] The compositions will include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc. Compositions of the invention may be used in combination with anticancer or other agents that are generally administered to a patient being treated for cancer. Adjuvants include preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0132] If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylalted hydroxytoluene, etc.

[0133] Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl

oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

[0134] One preferable route of administration is oral, using a convenient daily dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

[0135] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alignates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[0136] Solid dosage forms as described above can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

[0137] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. Such dosage forms are prepared, for example, by dissolving, dispersing, etc., a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like;

solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide; oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan; or mixtures of these substances, and the like, to thereby form a solution or suspension.

[0138] Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

[0139] Compositions for rectal administrations are, for example, suppositories that can be prepared by mixing the compounds of the present invention with for example suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt while in a suitable body cavity and release the active component therein.

[0140] Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

[0141] Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

[0142] Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, or a

pharmaceutically acceptable salt thereof, for treatment of a disease-state in accordance with the teachings of this invention.

[0143] The invention is used to make compounds, or their pharmaceutically acceptable salts, that are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease-states, and the host undergoing therapy. The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kilograms, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is an example. The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well known to one of ordinary skill in the art.

[0144] Abbreviations and their Definitions

The following abbreviations and terms have the indicated meanings throughout:

Abbreviation	Meaning
Ac	acetyl
ATP	adenosine triphosphate
BNB	4-bromomethyl-3-nitrobenzoic acid
Boc	t-butyloxy carbonyl
br	broad
Bu	butyl
°C	degrees Celsius
c-	cyclo
CBZ	CarboBenZoxy = benzyloxycarbonyl
d	doublet

Abbreviation	Meaning
dd	doublet of doublet
dt	doublet of triplet
DBU	Diazabicyclo[5.4.0]undec-7-ere
DCM	dichloromethane = methylene chloride = CH_2Cl_2
DCE	dichloroethylene
DEAD	diethyl azodicarboxylate
DIC	diisopropylcarbodiimide
DIEA	N,N-diisopropylethyl amine
DMAC	N,N-dimethylacetamide
DMAP	4-N,N-dimethylaminopyridine
DMF	N,N-dimethylfonnamide
DMSO	dimethyl sulfoxide
DVB	1,4-divinylbenzene
EEDQ	2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
EI	Electron Impact ionization
Et	ethyl
Fmoc	9-fluorenylmethoxycarbonyl
g	gram(s)
GC	gas chromatography
h or hr	hour(s)
HATU	0-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	hexamethyldisilazane
HOAc	acetic acid
HOBt	hydroxybenzotriazole
HPLC	high pressure liquid chromatography
L	liter(s)
M	molar or molarity
m	multiplet
Me	methyl

Abbreviation	Meaning
mesyl	methanesulfonyl
mg	milligram(s)
MHz	megahertz (frequency)
Min	minute(s)
mL	milliliter(s)
mM	millimolar
mmol	millimole(s)
mol	mole(s)
MS	mass spectral analysis
MTBE	methyl t-butyl ether
N	normal or normality
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
nM	nanomolar
NMO	N-methylmorpholine oxide
NMR	nuclear magnetic resonance spectroscopy
PEG	polyethylene glycol
pEY	poly-glutamine, tyrosine
Ph	phenyl
PhOH	phenol
PfP	pentafluorophenol
PfPy	pentafluoropyridine
PPTS	Pyridinium p-toluenesulfonate
Py	pyridine
PyBroP	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
q	quartet
RT	Room temperature
Sat'd	saturated
s	singlet

Abbreviation	Meaning
s-	secondary
t-	tertiary
t or tr	triplet
TBDMS	t-butyldimethylsilyl
TES	triethylsilane
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMOF	trimethyl orthoformate
TMS	trimethylsilyl
tosyl	p-toluenesulfonyl
Trt	triphenylmethyl
uL	microliter(s)
uM	Micromole(s) or micromolar

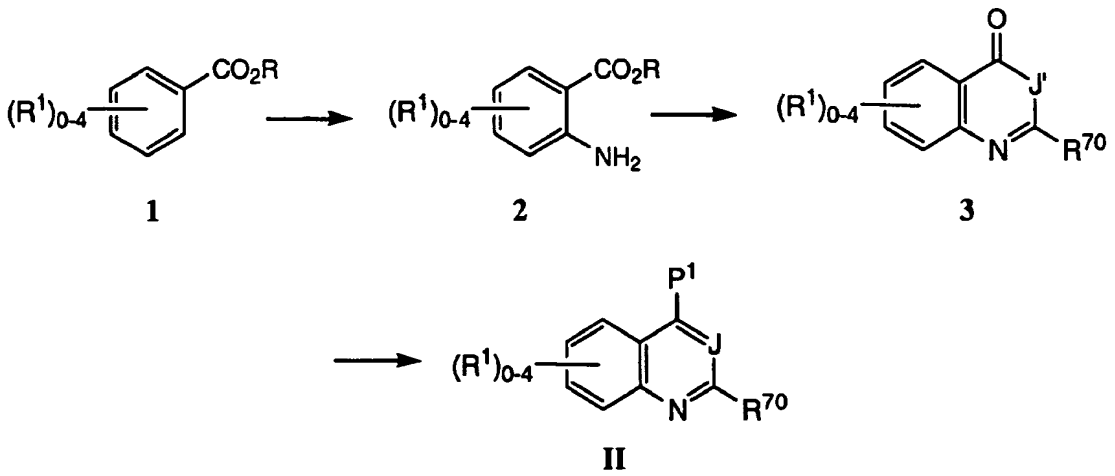
Synthesis of Compounds

[0145] Schemes 1 – 2 depict generalized synthetic routes to show the process of the invention to make compounds of Formual **I** and is not intended to be limiting. More specifically, Schemes 1 - 2 depict convergent syntheses of quinoline and quinazoline compounds as described herein. Specific examples are described subsequently to this general synthetic description so as to allow one of ordinary skill in the art to practice the invention.

[0146] Referring to Scheme 1, a benzoic ester **1** for example, where R is typically but not necessarily a methyl radical and R^1 is typically but not necessarily one or more alkoxy or hydroxy groups. In a typical synthesis, at least one of R^1 within scheme 1 is a hydroxyl which is converted via one or more steps to a group important to the activity of the compounds as described as kinase modulators. Preferably, but not necessarily, this group is complete once the synthesis of **II** is complete. By building desired complexity into **II** prior to combination with **III**, convergent synthesis advantages over serial synthesis are realized more fully. Regioselective aromatic ring nitration, and reduction of the corresponding nitro group, are carried out in a regio- and chemoselective manner by methods well known in the art to give

anthranilate derivative **2**. Formation of quinazoline or quinoline 4-one **3** is carried out by methods well known in the art. For example by heating **2** in formamide solution in the presence of ammonium formate, or by heating **2** with formamidine hydrochloride, the quinazoline-4-one analog is made. In another example **2** is treated, for example, with ethyl formate under basic conditions followed by acidification and isolation to form the 4-hydroxy quinoline analog (a tautomer of the 4-one). In this scheme J' represents either carbon or nitrogen atom with the appropriate number of hydrogens to fill their respective normal valence bonding schemes; J' is a precursor to J. Radicals J and R^{70} are in accord with Formula **I**. Introduction of 4-position functionality is carried out by methods known in the art. For example, 4-one **3** is converted to **II**, where "P^1" represents a suitable leaving group (in accord with Formula **I**), e.g. chlorine (via dehydration/chlorination of **3** to give **II**). In another example, a 4-hydroxy analog is converted to a sulfonyl ester, e.g. the trifluoromethane sulfonate.

Scheme 1

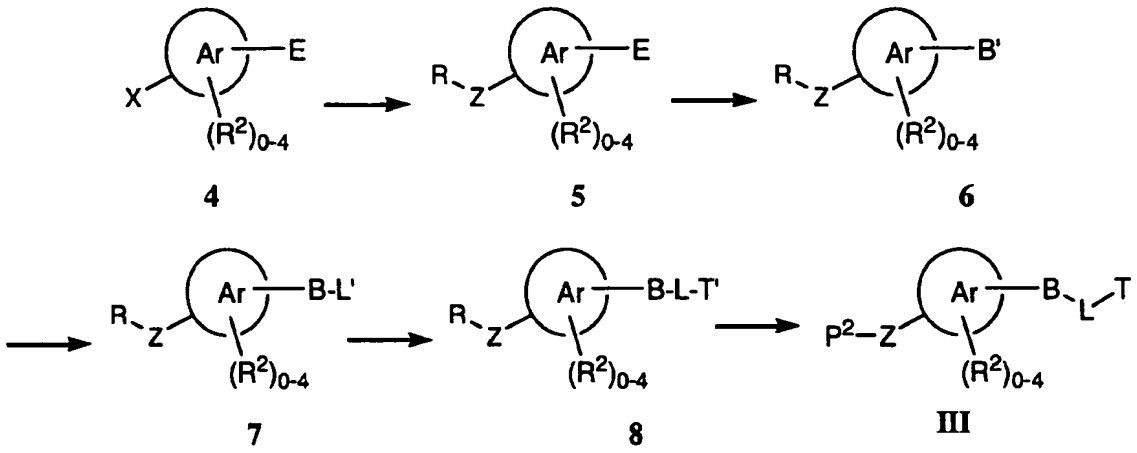


1 **2** **3** **II**

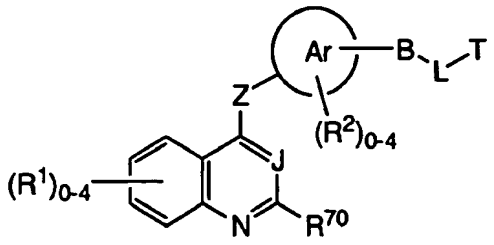
[0147] Scheme 2 shows a general route used to make compounds of Formula **III**. For example, aromatic compound **4**, where "X" is a leaving group, such as fluorine and "E" is an electron withdrawing group such as nitro, is converted to **5** by reaction with a range of nucleophiles, e.g. amines, alcohols, and thiols (where "Z" is oxygen, nitrogen (substituted or not), or sulfur). In this case, "R" represents a removable group, for example benzyl. In a typical synthesis, after formation of **5**, group "E" is either left "as is" or converted at some subsequent stage to a derivative thereof. In the example depicted, E is converted to B', a precursor to B in accord with Formula **I**, to make **6**. For example if E is a nitro, then B' could

might be an amino group, made via reduction of the nitro group. Structure **6** may be further derivitized by synthesis of –B-L-T in accord with formula **I**. In scheme 2, this is depicted as a serial process whereby L', a precursor to L, is introduced to give **7**, followed by introduction of T' (a precursor to T) to give **8**. In some cases, -L-T is preformed and appended to B. One of ordinary skill in the art would appreciate that variations on any of the above steps are possible. Compound **8** is converted to **III** via conversion of T' to T and introduction of P^2 (for example, when R is benzyl, removal of the benzyl after completion of –B-L-T).

Scheme 2



[0148] As discussed above, the invention encompasses combination of **II** and **III** to make compounds of Formula **I**. Because of the diversity and complexity of compounds previously described for kinase modulation (*vide supra*), methods of the invention provide advantages to serial synthesis.



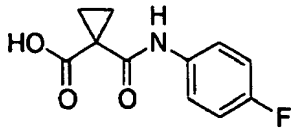
I

Examples

[0149] The following examples serve to more fully describe the manner of using the above-described invention, as well as to set forth the best modes contemplated for carrying out

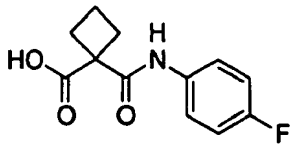
various aspects of the invention. It is understood that these examples in no way serve to limit the true scope of this invention, but rather are presented for illustrative purposes. All references cited herein are incorporated by reference in their entirety. Generally, each example set out below describes a multi-step synthesis as outlined above.

Example 1



[0150] **1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid**. The title compound was prepared based on a modified procedure of Shih and Rankin [*Synthetic Communications*, **1996**, 26(4), 833-836]: To a mixture of cyclopropane-1,1-dicarboxylic acid (21.2 g, 0.163 mol, 1.0 eq.) in anhydrous THF (200 mL) under nitrogen was added dropwise triethylamine (16.49 g, 0.163 mol, 1.0 eq.) with stirring for 30 minutes at 0°C, followed by the addition of thionyl chloride (19.39 g, 0.163 mol, 1.0 eq.) with stirring for another 30 minutes at 0°C. To the resulting mixture under nitrogen was added dropwise a solution of 4-fluoroaniline (19.92 g, 0.179 mol, 1.1 eq.) in anhydrous THF (100 mL) with stirring for 1.5 hours at 0°C. The reaction mixture was diluted with ethyl acetate and washed with 1N NaOH. The layers were separated, and the ethyl acetate layer was concentrated in vacuo to give a brownish solid. The brownish solid was washed with small amount of cold ethyl acetate, filtered and dried under vacuum to yield 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid as a white solid (23.71 g, 65.18%). ^{1}H NMR (400 MHz, CD_3OD): 7.57-7.53 (m, 2H), 7.05-7.00 (m, 2H) 1.46-1.43 (m, 2H), 1.40-1.37 (m, 2H).

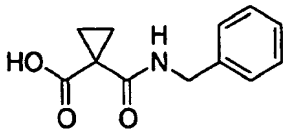
Example 2



[0151] **1-(4-Fluoro-phenylcarbamoyl)-cyclobutanecarboxylic acid.** To a mixture of cyclobutane-1,1-dicarboxylic acid (10.0 g, 69.4 mmol, 1.0 eq.) in anhydrous THF (100 mL) under nitrogen was added dropwise triethylamine (7.02 g, 69.4 mmol, 1.0 eq.) with stirring for 30 minutes at 0°C, followed by the addition of thionyl chloride (8.25 g, 69.4 mmol, 1.0

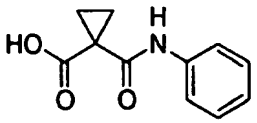
eq.) with stirring for another 30 minutes at 0°C. To the resulting mixture under nitrogen was added dropwise a solution of 4-fluoroaniline (8.48 g, 76.3 mmol, 1.1 eq.) in anhydrous THF (50 mL) with stirring for 1.5 hours at 0°C. The reaction mixture was diluted with ethyl acetate and extracted with 2N NaOH. The aqueous phase was titrated with 2N HCl to pH 1-2 and then extracted with ethyl acetate. The organic phase was dried with sodium sulfate and concentrated in vacuo to give 1-(4-fluoro-phenylcarbamoyl)-cyclobutanecarboxylic acid as a light pink solid (5.75 g, 34.9%). ^{1}H NMR (400 MHz, $CDCl_3$ w/1drop CD_3OD): 7.53-7.48 (m, 2H), 7.06-7.00 (m, 2H), 2.81-2.63 (m, 4H), 2.14-2.02 (m, 2H).

Example 3



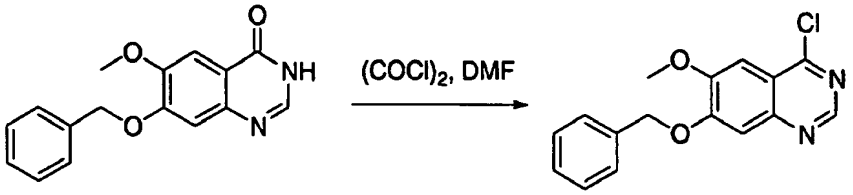
[0152] 1-Benzylcarbamoyl-cyclopropanecarboxylic acid. The title compound was prepared based on a modified procedure of Shih and Rankin [*Synthetic Communications*, **1996**, 26(4), 833-836]: To a mixture of cyclopropane-1,1-dicarboxylic acid (5.0 g, 38.4 mmol, 1.0 eq.) in anhydrous THF (50 mL) under nitrogen was added dropwise triethylamine (3.89 g, 38.4 mmol, 1.0 eq.) with stirring for 30 minutes at 0°C, followed by the addition of thionyl chloride (4.57 g, 38.4 mmol, 1.0 eq.) with stirring for another 30 minutes at 0°C. To the resulting mixture under nitrogen was added dropwise a solution of benzylamine **5** (4.53 g, 42.3 mmol, 1.1 eq.) in anhydrous THF (25 mL) with stirring for 1.5 hours at 0°C. The reaction mixture was diluted with ethyl acetate and extracted with 2N NaOH (to pH 10). The aqueous phase was titrated with 2N HCl to pH 1-2 and then extracted with ethyl acetate. The organic phase was dried with sodium sulfate and concentrated in vacuo to give 1-Benzylcarbamoyl-cyclopropanecarboxylic acid as a white solid (4.39 g, 52.15%). ^{1}H NMR (400 MHz, $CDCl_3$): 8.44 (br s, 1H), 7.37-7.33 (m, 2H), 7.32-7.26 (m, 3H), 1.82-1.70 (m, 4H).

Example 4



[0153] **1-Phenylcarbamoyl-cyclopropanecarboxylic acid.** To a mixture of cyclopropane-1,1-dicarboxylic acid (5.29 g, 40.7 mmol, 1.0 eq.) in anhydrous THF (50 mL) under nitrogen was added dropwise triethylamine (4.12 g, 40.7 mmol, 1.0 eq.) with stirring for 30 minutes at 0°C, followed by the addition of thionyl chloride (4.84 g, 40.7 mmol, 1.0 eq.) with stirring for another 30 minutes at 0°C. To the resulting mixture under nitrogen was added dropwise a solution of phenylamine 9 (4.17 g, 44.8 mmol, 1.1 eq.) in anhydrous THF (25 mL) with stirring for 1.5 hours at 0°C. The reaction mixture was diluted with ethyl acetate and extracted with 2N NaOH (to pH >10). The aqueous phase was titrated with 2N HCl to pH 1-2 and then extracted with ethyl acetate. The organic phase was dried with sodium sulfate and concentrated in vacuo to give 1-phenylcarbamoyl-cyclopropanecarboxylic acid as a white solid (5.08 g, 60.8%). ^{1}H NMR (400 MHz, $CDCl_3$): 10.50 (br s, 1H), 7.56-7.54 (m, 2H), 7.35-7.31 (m, 2H), 7.15-7.10 (m, 1H), 1.94-1.91 (m, 2H), 1.82-1.79 (m, 2H).

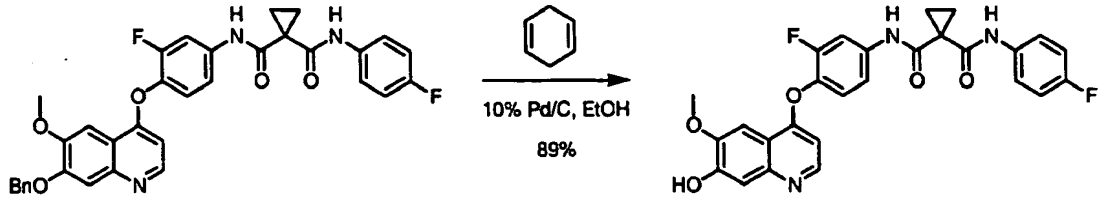
Example 5



[0154] **7-Benzyloxy-4-chloro-6-methoxy-quinoline.** Dry DMF (8.0ml, 103mmol) was dissolved in dry $CHCl_3$ (40ml) and cooled in an ice bath. Oxalyl chloride (9.0ml, 105mmol) in CH_2Cl_2 (10ml) was added dropwise with stirring at 0C. When the bubbling had ceased, this solution was added slowly to an ice-cold solution of 7-benzyloxy-6-methoxy-3H-quinazolin-4-one (10.0g, 35.4mmol) in dry $CHCl_3$ (60ml) and the mixture was then heated to reflux for 2-3hrs. After cooling to room temperature, H_2O (100ml) was added and the phases were separated. The aqueous phase was further extracted with $CHCl_3$ (2x). The combined $CHCl_3$ extractions were washed with sat'd NaCl (1x), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (1:1 hexanes:EtOAc,

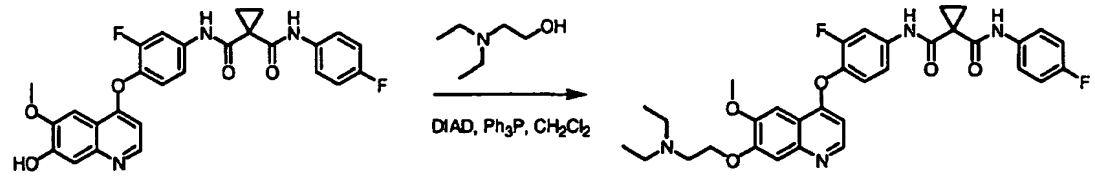
followed by 100%EtOAc) to give 7-benzyloxy-4-chloro-6-methoxy-quinoline (5.11g, 48%). LC/MS Calcd for $[M+H]^+$ 301.1, found 301.1.

Example 6



[0155] Cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide(4-fluoro-phenyl)-amide. To a solution of cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide (1.18g, 2.0 mmol) in EtOH (20 mL) was added 1,4-cyclohexadiene (2.0 mL, 20 mmol) and 10% Pd/C (300 mg). The reaction mixture was then heated to reflux and the stirring was continued for 2 h. It was cooled to room temperature, filtered through celite and washed with MeOH. The MeOH solution was then concentrated under reduced pressure. The residue was taken into EtOAc (200 mL). The EtOAc solution was washed with water, and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave 900 mg (89%) of the crude product (90% purity by analytical HPLC), which was used in the next reaction without further purification.

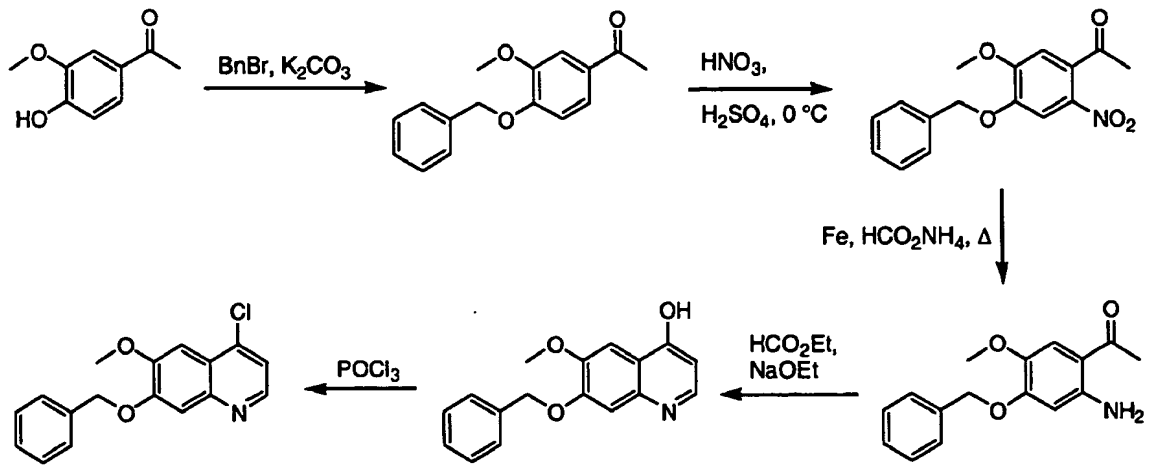
Example 7



[0156] N-(4-{[7-{[2-(Diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a mixture of cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide(4-fluoro-phenyl)-amide (186 mg, 0.36 mmol) in CH_2Cl_2 (10 mL) was added 2-(diethylamino)ethanol (63 mg, 0.54 mmol), and PPh_3 (141 mg, 0.54 mmol). DIAD (109 mg,

0.54 mmol) was then added as a CH_2Cl_2 (1 mL) solution. The resulted solution was stirred at room temperature for 2 h and the solvent was removed under reduced pressure. To the residue was added 1 N HCl (50 mL), and it was washed with EtOAc (50 mL x 2). The aqueous phase was basified by adding 15% NaOH aqueous solution until pH =11-13, and then extracted with ether (50 mL x 2). The combined organic layer was dried (MgSO4), and concentrated in vacuo. The residue was purified on preparative HPLC to give N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluoro-phenyl)cyclopropane-1,1-dicarboxamide (74 mg, 34%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (br s, 1 H), 10.02 (br s, 1 H), 8.47 (d, J = 5.2 Hz, 1 H), 7.91 (br d, J = 13.9 Hz, 1 H), 7.54-7.52 (m, 2 H), 7.55-7.50 (m, 1 H), 7.52 (s, 1 H), 7.50-7.40 (m, 1 H), 7.41 (s, 1 H), 7.16 (br t, J = 8.7 Hz, 2 H), 6.41 (br d, J = 4.7 Hz, 1 H), 4.18 (t, J = 6.0 Hz, 2 H), 3.94 (s, 3 H), 2.87 (br t, J = 6.3 Hz, 2 H), 2.59 (q, J = 7.1 Hz, 4 H), 1.47 (br s, 4 H), 1.00 (t, J = 7.0 Hz, 6 H).

Example 8



[0157] 1-(4-Benzyloxy-3-methoxyphenyl)ethanone. A solution of 4-hydroxy-3-methoxyacetophenone (40 g, 240 mmol), benzyl bromide (31.4 mL, 260 mmol) and potassium carbonate (99.6 g, 360 mmol) in DMF (800 mL) was heated to 40 °C overnight. The solution was cooled to room temperature, poured over ice and the resultant solid was filtered. This material was washed with water and dried to give 1-(4-benzyloxy-3-methoxyphenyl)ethanone (61 g, 99 %).

[0158] **1-(4-Benzyloxy-5-methoxy-2-nitrophenyl)ethanone.** A stirred solution of 1-(4-benzyloxy-3-methoxyphenyl)ethanone (51.3 g, 200 mmol) in dichloromethane (750 mL) was cooled to 0 °C. Nitric acid (90 %, 14 mL, 300 mmol) was added dropwise to the cooled solution over 20 min. Sulfuric acid (96.2 %, 16.3 mL, 300 mmol) was then added dropwise over 40 min at 0 °C. Additional nitric acid (9.4 mL, 200 mmol) was added dropwise over 20 min. The reaction mixture was washed with water (3 x 200 mL), and saturated sodium bicarbonate (4 x 200 mL, or until neutral). The organic layer was dried over Na_2SO_4 and concentrated. The crude mixture was recrystallized from DMF to give 1-(4-benzyloxy-5-methoxy-2-nitrophenyl)ethanone (36 g, 60 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.45-7.33 (m, 5H), 6.74 (s, 1H), 5.21 (s, 2H), 3.97 (s, 3H), 2.49 (s, 3H).

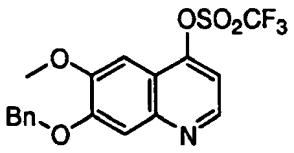
[0159] **1-(2-Amino-4-benzyloxy-5-methoxyphenyl)ethanone.** A mixture of iron powder (27 g, 0.48 g atoms), ammonium formate (31 g, 500 mmol), 1-(4-benzyloxy-5-methoxy-2-nitrophenyl)ethanone (36 g, 120 mmol), toluene (500 mL) and water (500 mL) was heated to reflux overnight. The mixture was filtered through celite and washed with ethyl acetate. The combined organic layers were washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated to afford 1-(2-amino-4-benzyloxy-5-methoxyphenyl)ethanone (29.3 g, 90 %). ^{1}H NMR ($CDCl_3$): δ 7.41-7.30 (m, 5H), 7.13 (s, 1H), 6.16 (br s, 2H), 6.10 (s, 1H), 5.13 (s, 2H), 3.83 (s, 3H), 2.51 (s, 3H). LC/MS (M+H = 272).

[0160] **7-Benzyloxy-6-methoxyquinolin-4-ol.** Sodium ethoxide (74.8 g, 1.1 mol) was added to a solution of 1-(2-amino-4-benzyloxy-5-methoxyphenyl)ethanone (29.3 g, 108 mmol) in DME (700 mL) and stirred for 30 min. Ethyl formate (44 mL, 540 mmol) was added and the mixture was stirred overnight (in case of incomplete reaction, additional sodium ethoxide can be added and the reaction monitored by LC/MS). After the reaction was complete, the mixture was diluted with water (40 mL) and acidified to neutral pH with 1M HCl. The solid was filtered, washed with water and dried to afford 7-benzyloxy-6-methoxyquinolin-4-ol (22 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.7 (br s, 1H), 7.70 (s, 1H), 7.49-7.46 (t, 1H), 7.43-7.41 (br d, 2H), 7.37-7.33 (t, 2H), 7.30-7.28 (d, 1H), 6.84 (s, 1H), 6.21-6.19 (d, 1H), 5.21 (s, 2H), 3.96 (s, 3H). LC/MS (M+H = 282).

[0161] **7-Benzyloxy-4-chloro-6-methoxyquinoline.** Phosphorus oxychloride (300 mL) was added to 7-benzyloxy-6-methoxyquinolin-4-ol (40 g, 140 mmol) and the mixture heated to reflux for 2 h. The mixture was carefully poured into a mixture of ice and sodium carbonate.

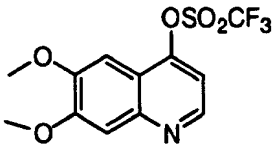
The solution was adjusted to pH 8 with the addition of solid sodium bicarbonate and stirred at room temperature overnight. The solid was filtered and washed with water and dried to give 7-benzyloxy-4-chloro-6-methoxyquinoline as a pale brown solid (40.2 g, 95%). ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.61 (s, 1H), 7.57-7.37 (m, 8H), 5.32 (s, 2H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 152.4, 151.5, 148.5, 146.2, 139.6, 137.0, 129.2, 128.8, 121.7, 120.4, 110.1, 101.9, 70.8, 56.5; IR (cm^{-1}): 2359, 2341, 1506, 1456, 1435, 1252, 1227, 1146, 999, 845, 752, 698, 667; LC/MS (M+H = 300).

Example 9



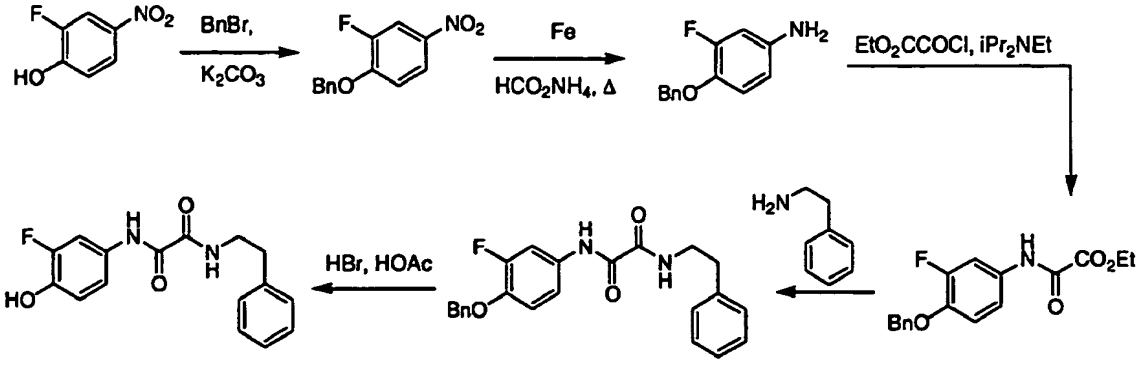
[0162] **Trifluoromethanesulfonic acid 7-benzyloxy-6-methoxy-quinolin-4-yl ester.** To a dry 2L RBF containing 7-benzyloxy-6-methoxyquinolin-4-ol (75.3 g, 267 mmol) was added DCM (1 L), 4-dimethylaminopyridine (3.28 g, 26.8 mmol) and 2,6-lutidine (62 mL, 534 mmol). The mixture was cooled to –20°C by controlled addition of dry ice to an acetone bath. Trifluoromethanesulfonyl chloride (37 mL, 350 mmol) was added dropwise to the cooled solution with magnetic stirring over 25 minutes. After addition was complete, the mixture was stirred in bath for 20 minutes, then at room temperature for 3 hours. LCMS indicated reaction completion. The reaction mixture was concentrated *in vacuo* and placed under high vacuum to remove residual 2,6-lutidine. To the resulting brown solids was added methanol (3.5 L). The resulting slurry was stirred with mechanical stirrer for 30 min before adding water (1.5 L). The solids were isolated by filtration, followed by a water wash. The resulting solid was dried under high vacuum overnight yielding trifluoromethanesulfonic acid 7-benzyloxy-6-methoxy-quinolin-4-yl ester as a light brown solid (92.2 g, 83.8%). ^{1}H NMR (400MHz, DMSO, d_6): δ 8.82 (d, 1H), 7.67 (s, 1H), 7.59 (d, 1H), 7.54-7.52 (m, 2H), 7.46-7.42 (m, 2H), 7.39-7.36 (m, 1H), 7.23 (s, 1H), 5.35 (s, 2H), 3.97 (s, 3H). LC/MS: M+H = 414.

Example 10



[0163] **Trifluoromethanesulfonic acid 6,7-dimethoxyquinolin-4-yl ester from 6,7-Dimethoxy-quinolin-4-ol.** To a dry 1L RBF containing 6,7-dimethoxy-quinolin-4-ol (20.9 g, 102 mmol), which can be prepared according to the procedure of Riegel, B. *(J. Amer. Chem. Soc.* **1946**, *68*, 1264), was added DCM (500 mL), 4-dimethylaminopyridine (1.24 g, 10 mmol) and 2,6-lutidine (24 mL, 204 mmol). The mixture was vigorously stirred at RT. Trifluoromethanesulfonyl chloride (14 mL, 132 mmol) was added dropwise to the solution. After addition was complete, the mixture was stirred ice bath for 2 to 3 hrs. On LC/MS indicating the reaction completion, the reaction mixture was concentrated *in vacuo* and placed under high vacuum to remove residual 2,6-lutidine. To the resulting brown solids was added methanol (250 mL). The resulting slurry was stirred for 30 min before adding water (1 L). The solids were isolated by filtration, followed by a water wash. The resulting solid was dried under high vacuum overnight yielding trifluoromethanesulfonic acid 6, 7-dimethoxy-quinolin-4-yl ester as a light brown solid (27 g, 80%). ^{1}H NMR (400MHz, DMSO, d_6): δ 8.82 (d, 1H), 7.59 (m, 2H), 7.20 (s, 1H), 3.97 (d, 6H). LC/MS: M+H = 338.

Example 11



[0164] **1-Benzyloxy-2-fluoro-4-nitrobenzene.** A solution of 2-fluoro-4-nitrophenol (50.0 g, 318 mmol), benzyl bromide (42 mL, 350 mmol) and potassium carbonate (66.0 g, 478 mmol)

in DMF (200 mL) was heated to 40 °C overnight. The solution was cooled to room temperature, poured over ice and the resultant solid was filtered. This material was washed with water and dried to give 1-benzyloxy-2-fluoro-4-nitrobenzene (75.0 g, 95 %). ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.19-8.11 (m, 2H), 7.53-7.37 (m, 6H), 5.36 (s, 2H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 152.8, 152.4, 149.9, 140.9, 136.1, 129.3, 129.1, 128.7, 122.0, 115.2, 112.8, 112.6, 71.6; IR (cm^{-1}): 1499, 1346, 1279, 1211, 1142, 1072, 986, 885, 812, 789, 754, 742, 700, 648, 577.

[0165] **4-Benzyloxy-3-fluoroaniline.** A mixture of iron powder (45.2 g, 0.809 g atoms), ammonium formate (53.6 g, 0.850 mol), 1-benzyloxy-2-fluoro-4-nitrobenzene (50.0 g, 0.200 mol), toluene (400 mL) and water (400 mL) was heated to reflux overnight. The mixture was filtered through Celite and washed with hot ethyl acetate. The combined organic layers were washed with water and brine, then dried over sodium sulfate and concentrated to afford 4-benzyloxy-3-fluoroaniline (44 g, 100 %). ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.43-7.26 (m, 5H), 6.90 (dd, 1H), 6.49 (dd, 1H), 6.34 (m, 1H), 4.99 (br s, 2H), 4.98 (s, 2H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 171.1, 155.1, 152.7, 144.9, 138.0, 137.2, 129.6, 129.0, 128.5, 118.9, 110.0, 102.9, 72.5; IR (cm^{-1}): 1510, 1454, 1277, 1215, 1126, 1007, 957, 843, 800, 789, 739, 694, 604; LC/MS (M+H = 218).

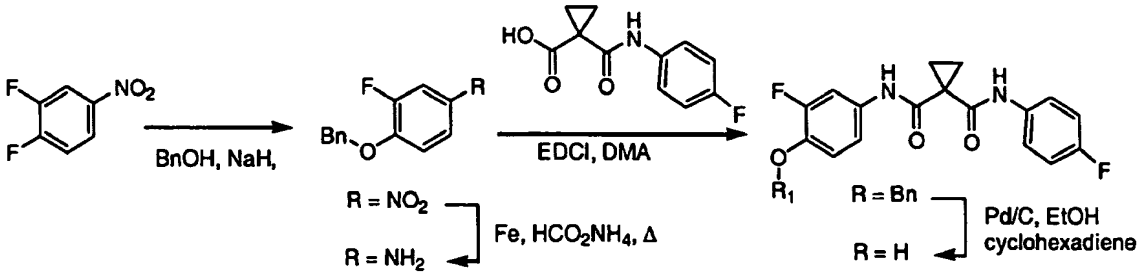
[0166] **Ethyl [(4-benzyloxy-3-fluorophenyl)amino](oxo)acetate.** Ethyl oxalyl chloride (44 mL, 390 mmol) was added to a solution of 4-benzyloxy-3-fluoroaniline (44 g, 180 mmol) in diisopropylethylamine (69 mL, 400 mmol) and stirred at room temperature for 15 min. The mixture was extracted with dichloromethane and washed with water and brine. The organic layer was dried over sodium sulfate and concentrated to afford ethyl [(4-benzyloxy-3-fluorophenyl)amino](oxo)acetate (58.4 g, 100 %). ^{1}H NMR (400 MHz, d_6-DMSO): δ 10.87 (s, 1H), 7.73 (d, 1H), 7.69 (d, 1H), 7.53 (d, 1H), 7.46-7.40 (m, 4H), 5.17 (s, 2H), 4.31 (q, 2H), 1.31(t, 3H); IR (cm^{-1}): 1732, 1705, 1558, 1541, 1508, 1456, 1273, 1186, 1167, 1101, 999, 858, 741, 694; LC/MS (M+H = 318).

[0167] ***N*-(4-Benzyloxy-3-flourophenyl)-*N'*-(2-phenylethyl)ethanediamide.** Phenethylamine (33 mL, 520 mmol) was added to ethyl [(4-benzyloxy-3-fluorophenyl)amino](oxo)acetate (81 g, 260 mmol) and the mixture was sonicated at room temperature for 30 min. The resulting solid was filtered, washed with water and dried to give *N*-(4-benzyloxy-3-flourophenyl)-*N'*-(2-phenylethyl)ethanediamide (100 g, 99 %). ^{1}H NMR

(400 MHz, d_6-DMSO): δ 10.72 (br s, 1H), 9.05 (m, 1H), 8.78 (m, 1H), 7.77 (m, 1H), 7.59 (m, 1H), 7.46-7.19 (m, 8H), 5.16 (m, 2H), 3.45 (m, 2H), 2.83 (m, 2H); IR (cm^{-1}): 2980, 2883, 1653, 1522, 1506, 1441, 1385, 1221, 1122, 951, 808, 746, 696, 584; LC/MS (M+H = 393).

[0168] ***N*-(3-Fluoro-4-hydroxyphenyl)-*N'*-(2-phenylethyl)ethanediamide.** A mixture of *N*-(4-benzyloxy-3-flourophenyl)-*N'*-(2-phenylethyl)ethanediamide (40 g, 100 mmol) and 38% hydrobromic acid in acetic acid (250 mL) was stirred at room temperature overnight. The resulting solid was filtered, washed with water and dried to give *N*-(3-fluoro-4-hydroxyphenyl)-*N'*-(2-phenylethyl)ethanediamide as a slightly yellow solid (30.6 g, 99 %yield). ^{1}H NMR (400 MHz, d_6-DMSO): δ 10.60 (s, 1H), 9.02 (t, 1H), 7.70 (d, 1H), 7.47 (d, 1H), 7.32-7.20 (m, 3H), 6.91 (t, 1H), 3.43 (m, 2H), 2.81 (m, 2H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 160.5, 158.8, 152.0, 149.6, 142.2, 139.8, 130.3, 129.3, 129.0, 126.8, 118.1, 117.4, 109.6, 109.3 IR (cm^{-1}): 3279, 1653, 1518, 1456, 1279, 1190, 742, 696, 584; LC/MS (M+H = 303).

Example 12



[0169] **1-Benzyloxy-2-fluoro-4-nitro-benzene.** To a slurry of sodium hydride (60% dispersion is oil, 693 mmol, 27.7 g) and dimethylacetamide (600 ml) was added benzyl alcohol (462 mmol, 48 ml) dropwise with stirring under N_2. The mixture was stirred for 1 hour at RT and then cooled to 0°C. 3,4-difluoronitrobenzene (508 mmol, 56.2 ml) was added to the cooled solution and stirred for 1 hour. Reaction mixture poured onto saturated ammonium chloride solution (800 ml) and stirred for 30 minutes, filtered and washed with water. The solid was stirred in ethyl acetate (500 mL), and filtered to give 54g of product. The ethyl acetate filtrate, after concentrated in vacuo, was triturated with diethyl ether (500 mL), sonicated for 2 hours, and filtered to give another 30g of product. The ether layer was concentrated and column purified using 5% EtOAc/hexanes as eluent to gave additional 15g

of product. The total yield of 1-benzyloxy-2-fluoro-4-nitro-benzene was 95g (83%). (Note: the product contains ca. 5% of 3,4-Bis-benzyloxy-nitrobenzene, which is carried into the next step without further purification.) ^{1}H NMR (400MHz, $CDCl_3$): δ 8.04 –8.00 (m, 2H), 7.43-7.37 (m, 5H), 7.08 (t, 1H), 5.26 (s, 2H).

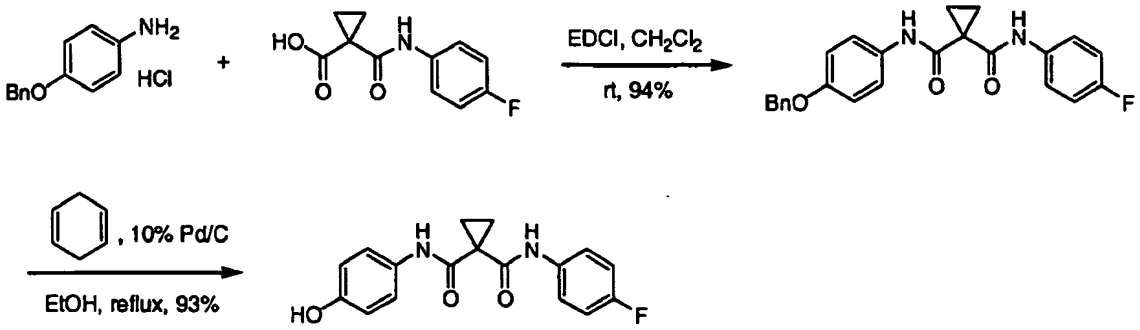
[0170] **4-Benzyloxy-3-fluoro-phenylamine.** A mixture of 1-benzyloxy-2-fluoro-4-nitro-benzene (44g, 178 mmol), toluene (400 ml), ammonium formate (35 g), iron (30 g), and water (400 ml) was heated to reflux with stirring overnight. The reaction mixture was filtered through celite and washed with ethyl acetate (400ml). The organic layer was separated and washed with brine (300 ml), dried over sodium sulfate and concentrated to give 4-benzyloxy-3-fluoro-phenylamine as an oil (33.7 g, 87%). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.41-7.29 (m, 5H), 6.79 (t, 1H), 6.45 (dd, 1H), 6.14 (dd, 1H), 5.02 (s, 2H), 3.50 (s, 2H). LC/MS: (M+1) 218.

[0171] **Cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-3-fluoro-phenyl)-amide (4-fluoro-phenyl)-amide.** To a stirred mixture of 4-benzyloxy-3-fluoro-phenylamine (155.3 mmol, 33.7 g), 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (170.8 mmol, 38.13 g) and anhydrous dichloromethane (600 ml) was added EDCI (233.9 mmol, 44.7 g) in portions. After stirring at RT for 1 hr, the reaction mixture was diluted with saturated sodium bicarbonate (400 ml) and stirred for 30 minutes. The precipitate was filtered and air dried to give the 1st crop of product. The biphasic filtrate was separated, and the organic phase was washed with brine (300 ml), dried over sodium sulfate, and concentrated. The residue was taken up in DCM (100 ml), stirred for 15 minutes, and filtered to give a 2nd crop of product. The combined yield of cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-3-fluoro-phenyl)-amide (4-fluoro-phenyl)-amide was 64.5 g (98%). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.92 (br s, 1H), 8.88 (br s, 1H), 7.50-7.32 (m, 8H), 7.06-7.02 (m, 3H), 6.97-6.92 (t, 1H), 5.13 (s, 2H), 1.65 (s, 4H). LC/MS: (M+1) 423.

[0172] **Cyclopropane-1,1-dicarboxylic acid (3-fluoro-4-hydroxy-phenyl)-amide (4-fluoro-phenyl)-amide.** A mixture of cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-3-fluoro-phenyl)-amide (4-fluoro-phenyl)-amide (152.8 mmol, 64.5), ethanol (800 ml), cyclohexadiene (764 mmol, 71 ml), and 10% Pd/C (2 g) was refluxed for 2 hours. Reaction mixture cooled and filtered through celite and washed with methanol. The combined filtrate was concentrated and stirred in 10% EtOAc/ether (350 ml). The resulting precipitate was

filtered and washed with ether to give a 1st crop of product. The filtrate was concentrated and stirred in DCM (150 ml) to give another precipitate, which was then filtered to give a 2nd crop of product. The combined yield of cyclopropane-1,1-dicarboxylic acid (3-fluoro-4-hydroxy-phenyl)-amide (4-fluoro-phenyl)-amide was 43 g (85%) in 95% purity by HPLC (UV @ 254 nm). ^{1}H NMR (400MHz, DMSO-D6): δ 10.07 (br s, 1H), 9.92 (br s, 1H), 9.64 (br s, 1H), 7.64-7.60 (m, 2H), 7.55-7.51 (m, 1H), 7.17-7.12 (m, 3H), 6.89-6.84 (t, 1H), 1.43 (s, 4H). LC/MS: (M+1) 333.

Example 13

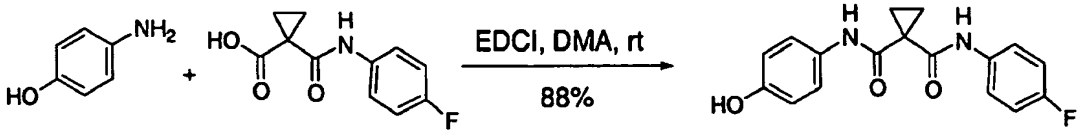


[0173] Cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-phenyl)-amide (4-fluoro-phenyl)-amide. To a 0 °C suspension of 4-benzyloxyaniline hydrochloride (47.0 g, 200 mmol) and 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (49.1 g, 220 mmol) in CH_2Cl_2 (400 mL) was added EDCI (38.2 g, 200 mmol). Stirring was continued at rt for 2-4 h until the reaction was complete. CH_2Cl_2 was removed under reduced pressure. H_2O (300 mL) and MeOH (200 mL) were added, and the resulting mixture was stirred at rt for 30 min. After filtration and wash with H_2O, the solid was transferred to another flask containing 300 mL of sat. aqueous $NaHCO_3$ solution. The mixture was stirred for another 30 min. The solid was filtered, washed with water, and dried over night on a lyophilizer, affording cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-phenyl)-amide (4-fluoro-phenyl)-amide (75.8g, 95% yield) as an off-white solid.

[0174] Cyclopropane-1,1-dicarboxylic acid (4-fluoro-phenyl)-amide (4-hydroxy-phenyl)-amide. To a refluxing mixture of cyclopropane-1,1-dicarboxylic acid (4-benzyloxy-phenyl)-amide (4-fluoro-phenyl)-amide (46 g, 113 mmol), 10% Pd/C (2 g) in EtOH (400 mL) was added dropwise 1,4-cyclohexadiene (62.7 mL, 678 mmol). Stirring was continued for 2-5 h

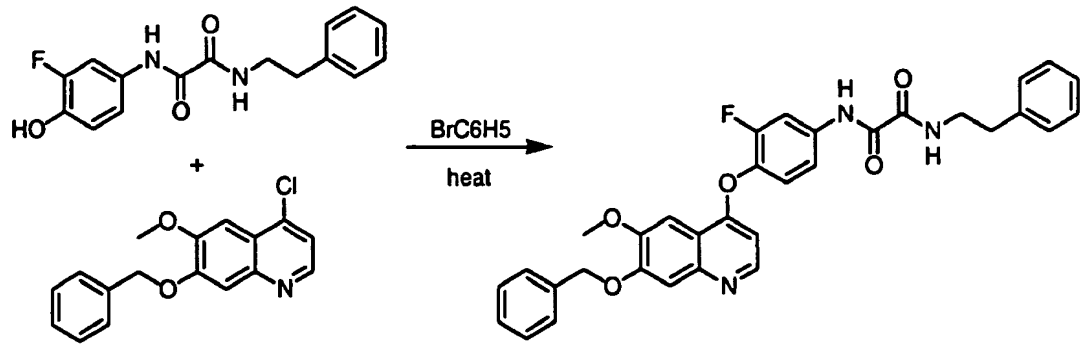
until the reaction was complete. The mixture was cooled to rt, filtered through celite, and washed with EtOH. The solution was then concentrated under reduced pressure. To the flask containing the crude product was added $CHCl_3$ (200 mL). The resulting suspension was stirred for 15 min at rt. The solid was filtered, and dried in the air to give cyclopropane-1,1-dicarboxylic acid (4-fluoro-phenyl)-amide (4-hydroxy-phenyl)-amide (34.4 g, 95%, yield).

Example 14



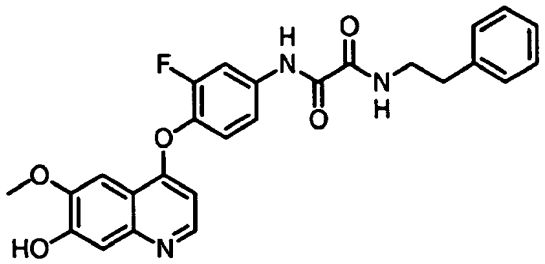
[0175] **Alternate Synthesis of Cyclopropane-1,1-dicarboxylic acid (4-fluoro-phenyl)-amide (4-hydroxy-phenyl)-amide.** To a solution of 4-aminophenol (2.93 g, 26.9 mmol) and 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (5.00 g, 22.4 mmol) in DMA (30 mL) was added EDCI (5.15 g, 26.9 mmol). The mixture was stirred vigorously until the reaction was complete (~ 3 h). With vigorous stirring, the reaction mixture was then poured into a flask containing sat. aqueous $NaHCO_3$ solution (200 mL). The stirring was continued for 1 h. The resulting suspension was then filtered. The solid was washed with water (50 mL), chloroform (50 mL) and dried under vacuum, affording 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (6.22g, 88% yield) as a powder (>95% purity by HPLC and ^1H NMR).

Example 15



[0176] ***N*-{4-[(7-Benzyloxy-6-methoxyquinolin-4-yl)oxy]-3-fluorophenyl}-*N'*-(2-phenylethyl)ethanediamide.** A mixture of 7-benzyloxy-4-chloro-6-methoxyquinoline (30 g, 100 mmol), *N*-(3-fluoro-4-hydroxyphenyl)-*N'*-(2-phenylethyl)ethanediamide (32 g, 106 mmol), DMAP (125 g, 1.02 mol) and bromobenzene (500 mL) was heated to reflux for 6 h. The mixture was cooled to room temperature and the bromobenzene was removed under reduced pressure. Methanol (500 mL) was added to the residue and the mixture was stirred at room temperature for 2 h. The resulting solid was filtered, washed with methanol and dried to give *N*-{4-[(7-benzyloxy-6-methoxyquinolin-4-yl)oxy]-3-fluorophenyl}-*N'*-(2-phenylethyl) ethanediamide (34 g, 61 %). ^{1}H NMR (400 MHz, d_6-DMSO): δ 11.05 (s, 1H), 9.15 (s, 1H), 8.47 (d, 1H), 8.05 (d, 1H), 7.84 (d, 1H), 7.56-6.36 (m, 13H), 6.46 (d, 1H), 5.32 (s, 2H), 3.97 (s, 3H), 3.47 (q, 2H), 2.86 (t, 2H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 160.5, 160.2, 159.9, 159.5, 155.2, 152.7, 152.2, 150.3, 149.6, 146.9, 139.7, 137.4, 137.3, 137.2, 137.1, 129.3, 129.2, 129.1, 129.0, 128.9, 128.7, 128.6, 126.9, 124.8, 117.9, 115.3, 109.9, 102.8, 99.8, 70.6, 56.5, 41.3, 35.2; IR (cm^{-1}): 1657, 1510, 1481, 1433, 1416, 1352, 1310, 1252, 1215, 1609, 986, 891, 868, 850, 742, 696; LC/MS (M+H = 566).

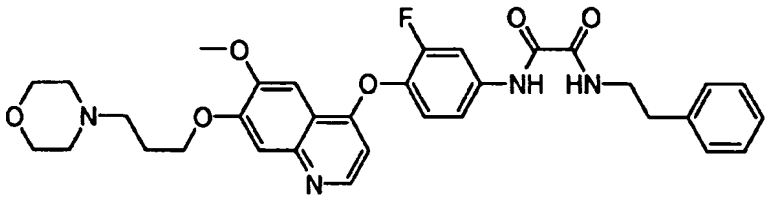
Example 16



[0177] ***N*-{3-Fluoro-4-[(7-hydroxy-6-methoxyquinolin-4-yl)oxy]phenyl}-*N'*-(2-phenylethyl)ethanediamide.** To a solution of *N*-{4-[(7-benzyloxy-6-methoxyquinolin-4-yl)oxy]-3-fluorophenyl}-*N'*-(2-phenylethyl)ethanediamide (32 g, 56 mmol) in methanol (200 mL), DMF (100 mL), dichloromethane (100 mL), ethyl acetate (100 mL) and acetic acid (5 mL) was added palladium hydroxide (4.2 g) and the mixture was shaken on a Parr hydrogenator under a hydrogen pressure of 45 psi for 4 h. The resulting suspension was filtered through celite and the solid residue was washed with boiling dichloromethane (2 L) and acetone (2 L). The combined filtrates were evaporated to yield *N*-{3-fluoro-4-[(7-hydroxy-6-methoxyquinolin-4-yl)oxy]phenyl}-*N'*-(2-phenylethyl)ethanediamide as an off-

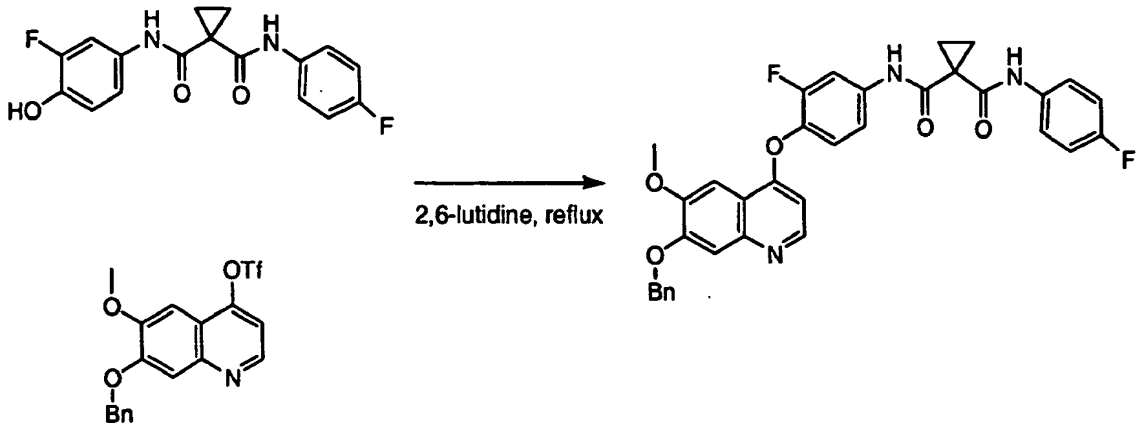
white solid (25.6 g, 95 %). ^{1}H NMR (400 MHz, d_6-DMSO): δ 11.06 (s, 1H), 10.25 (br s, 1H), 9.12 (t, 1H), 8.40 (d, 1H), 8.01 (dd, 1H), 7.50-7.44 (m, 2H), 7.31-7.23 (m, 6H), 6.39 (d, 1H), 3.95 (s, 3H), 2.85 (t, 2H), 2.50 (m, 2H); IR (cm-1): 1666, 1624, 1585, 1520, 1481, 1427, 1377, 1256, 1211, 1194, 1022, 880, 850, 839, 802, 750, 700; LC/MS (M+H = 476).

Example 17



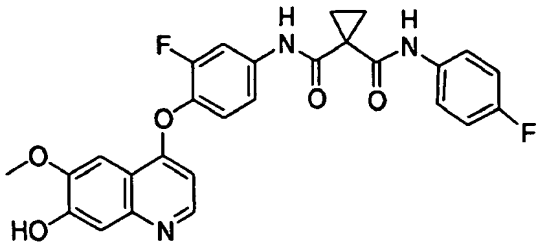
[0178] ***N*-(3-Fluoro-4-{[6-methoxy-7-(3-morpholin-4-ylpropoxy)quinolin-4-yl]oxy}phenyl)-*N'*-(2-phenylethyl)ethanediamide.** A solution of *N*-{3-fluoro-4-[(7-hydroxy-6-methoxyquinolin-4-yl)oxy]phenyl}-*N'*-(2-phenylethyl)ethanediamide (25.6 g, 54 mmol), *N*-(3-chloropropyl)morpholine hydrochloride (11.7 g, 592 mmol) and potassium carbonate (16.6 g, 120 mmol) in DMF (300 mL) was heated to 80 °C overnight. Upon cooling, a majority of the DMF (250 mL) was removed on a rotary evaporator, 5% aqueous LiCl (300 mL) was added and the mixture was sonicated at room temperature. The solid was filtered, suspended in 1N HCl and washed with ethyl acetate (2 x 300 mL). The solution was adjusted to pH 14 using 2N sodium hydroxide and subsequently extracted with dichloromethane (3 x 200 mL). The organic layer was dried over sodium sulfate, filtered and evaporated to give *N*-(3-fluoro-4-{[6-methoxy-7-(3-morpholin-4-ylpropoxy)quinolin-4-yl]oxy}phenyl)-*N'*-(2-phenylethyl)ethanediamide as a yellow solid (24 g, 74 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.37 (s, 1H), 8.46 (d, 1H), 7.81 (dd, 1H), 7.57 (t, 1H), 7.53 (s, 1H), 7.42 (s, 2H), 7.34-7.20 (m, 6H), 6.39 (d, 1H), 4.27 (t, 2H), 4.03 (s, 3H), 3.71 (m, 4H), 3.65 (q, 2H), 2.91 (t, 2H), 2.56 (br s, 4H), 2.13 (m, 2H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 160.1, 160.0, 159.5, 155.2, 152.7, 152.6, 150.2, 149.5, 147.1, 139.7, 137.3, 137.1, 129.3, 129.1, 126.9, 124.8, 117.9, 115.1, 109.2, 102.7, 99.6, 67.4, 66.9, 56.5, 55.5, 54.1, 41.3, 35.2, 26.4; IR (cm^{-1}): 1655, 1506, 1483, 1431, 1350, 1302, 1248, 1221, 1176, 1119, 864, 843, 804, 741, 700; LC/MS (M+H = 603).

Example 18



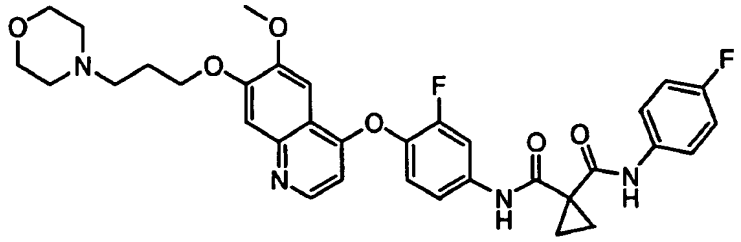
[0179] Cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide. To a flask containing cyclopropane-1,1-dicarboxylic acid (3-fluoro-4-hydroxy-phenyl)-amide (4-fluoro-phenyl)-amide (2.25 g, 6.7 mmol) and trifluoromethanesulfonic acid 7-benzyloxy-6-methoxy-quinolin-4-yl ester (1.87 g, 4.5 mmol) was added dry 2,6-lutidine (9 mL). The reaction mixture was heated to reflux (143°C) with vigorous stirring. The reaction progress was monitored by LC-MS. 2,6-Lutidine was removed under reduced pressure when the reaction was complete (about 6 h). The residue was treated with charcoal (1.5 g) in refluxing EtOAc (50 mL) for 15 min, and filtered through celite. The volume of the filtrate was reduced to about 20 mL and was added 20 mL of 1 N HCl. The crude product precipitated as the HCl salt, which was filtered and washed with EtOAc and H_2O (88% purity by analytical HPLC). The HCl salt was free-based with saturated aqueous $NaHCO_3$ solution. Further purification by column chromatography (hexans:EtOAc = 1:4) gave cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide as an off-white solid (1.3 g, 48% yield. ^{1}H NMR (400 MHz, DMSO, d_6): 10.41 (s, 1H), 10.02 (s, 1H), 8.48 (d, 1H), 7.92 (dd, 1H), 7.65 (m, 2H), 7.54 (m, 5H), 7.41 (m, 4H), 7.17 (m, 2H), 6.43 (d, 1H), 5.32 (s, 2H), 3.97 (s, 3H), 1.48 (m, 4H). LC/MS Calcd for $[M+H]^+$ 596.2, found 596.3.

Example 19



[0180] **Cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide.** To a solution of the cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide (22.4 g, 37.6 mmol) in EtOH (340 mL) was added 1,4-cyclohexadiene (35 mL, 376 mmol) and 10% Pd/C (2.08 g). The reaction mixture was then heated at 65°C with stirring for 3 h (Caution: H_2 gas is released from the reaction). It was then allowed to cool to room temperature, and filtered through celite follwed by a MeOH wash. The solution was then concentrated under reduced pressure. The yellow residue was taken into EtOAc (1 L). The EtOAc solution was washed with water (1X), brine (2X), dried over $MgSO_4$ and concentrated *in vacuo*. Cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide was obtained as a yellow solid (17.3 g, 91.1% yield), which were carried on to the next reaction without further purification. ^{1}H NMR (400 MHz, DMSO, d6): 10.39 (s, 1H), 10.15 (s, 1H), 10.00 (s, 1H), 8.38 (d, 1H), 7.88 (dd, 1H), 7.63 (m, 2H), 7.50 (m, 2H), 7.40 (t, 1H), 7.27 (s, 1H), 7.14 (m, 2H), 6.33 (d, 1H), 3.95 (s, 3H), 1.47 (m, 4H). LC/MS Calcd for $[M+H]^+$ 506.2, found 506.3. Anal. HPLC: 99.4% pure.

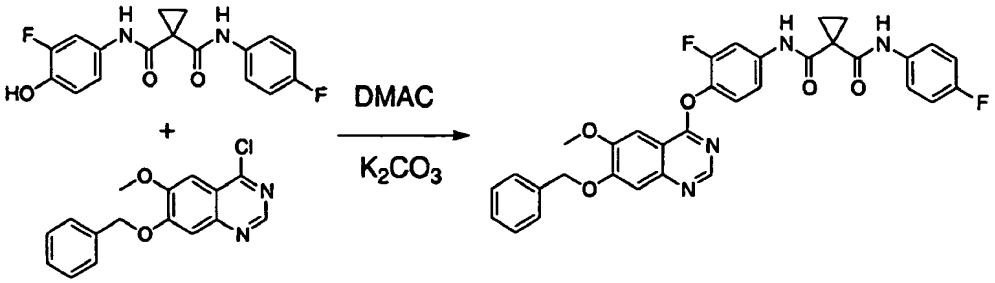
Example 20



[0181] *N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a mechanically stirred slurry of cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-

quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (16.6 g, 32.8 mmol) and potassium carbonate (13.6 g, 98.6 mmol) in DMF (250 mL) was added 4-(3-chloropropyl)-morpholine hydrochloride (13, 7.92 g, 39.6 mmol). The resulting mixture was heated at 90°C for 5 hours (until phenol completely consumed). The reaction mixture was allowed to cool to room temperature, then dumped into water (900 mL), followed by extraction with EtOAc (3X). The combined extracts were washed with 5% LiCl (aq.) (3X) and brine (1X) followed by drying over MgSO4 and concentration in vacuo. The crude (18.8g) obtained as brown solid was further purified by flash chromatography [silica gel, 4-stage gradient system: 1) EtOAc; 2) EtOAc:MeOH:7N NH_3/MeOH (95:5:0.5); 3) DCM:MeOH:7N NH3/MeOH (95:5:0.5); 4) DCM:MeOH: 7N NH_3/MeOH (93:8:1)], affording N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide was obtained as an off white solid (15.0 g, 72% yield). 1H NMR (400 MHz, DMSO-d6): 10.41 (s, 1H), 10.02 (s, 1H), 8.47 (d, 1H), 7.91 (dd, 1H), 7.65 (m, 2H), 7.53 (m, 2H), 7.42 (t, 1H), 7.40 (s, 1H), 7.16 (m, 2H), 6.42 (d, 1H), 4.20 (t, 2H), 3.96 (s, 3H), 3.59 (t, 4H), 2.47 (t, 2H), 2.39 (br, s, 4H), 1.98 (m, 2H), 1.48 (m, 4H). LC/MS Calcd for [M+H]+ 633.3, found 633.0.

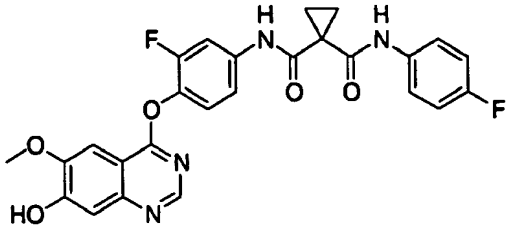
Example 21



[0182] Cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinazolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide: A mixture of 7-benzyloxy-4-chloro-6-methoxy-quinazoline (5 g, 16.67 mmol), cyclopropane-1,1-dicarboxylic acid (3-fluoro-4-hydroxy-phenyl)-amide (4-fluoro-phenyl)-amide (8.3 g, 25 mmol), potassium carbonate (125 mmol, 17.25 g), and dimethylacetamide (125 ml) was heated 50° C with stirring for 16h. Reaction mixture was poured onto ice/water (600 ml) and stirred for 30 minutes, and filtered. The solid was dissolved in ethyl acetate and washed with water (1x), brine, and concentrated. The crude was purified on silica get column eluting with 30% acetone in hexanes to yield

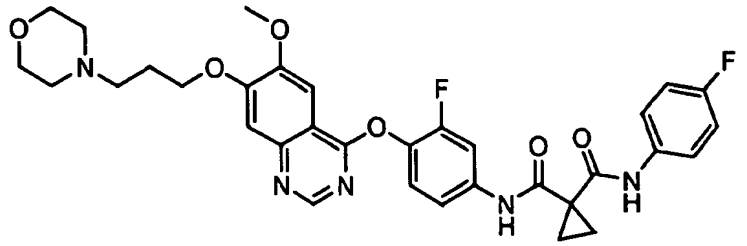
cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinazolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide (7.5 g, 76%). ^{1}H NMR ($CDCl_3$): 8.64 (1H, br. s), 8.55 (1H, s), 8.33 (1H, br. s), 7.74-7.71 (1H, dd), 7.54 (1H, s), 7.48-7.33 (8H, m), 7.31-7.24 (2H, m), 7.06-7.02 (2H, m), 5.32 (2H, s), 4.06 (3H, s), 1.77-1.74 (2H, m), 1.63-1.61 (2H, m).

Example 22



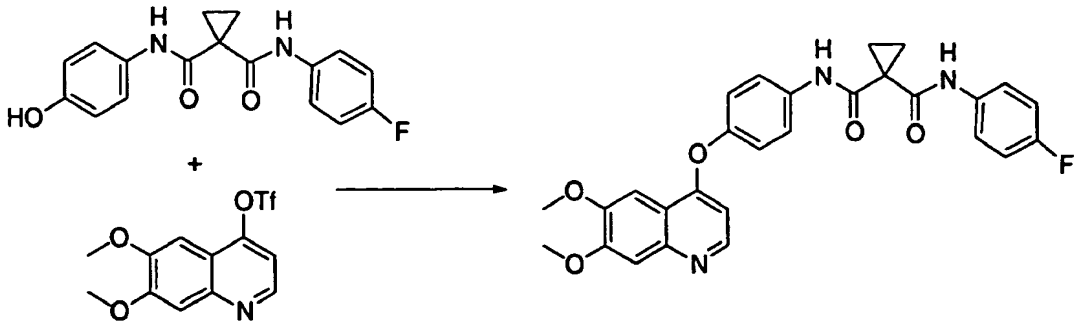
[0183] **Cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide.** To a mixture of cyclopropane-1,1-dicarboxylic acid [4-(7-benzyloxy-6-methoxy-quinazolin-4-yloxy)-3-fluoro-phenyl]-amide (4-fluoro-phenyl)-amide (7.5 g, 12.6 mmol), acetic acid (few drops), dichloromethane (50 ml) and methanol (100 ml) was added 10% Pd/C (700 mg). The mixture was agitated in hydrogen gas (40 psi) until the reaction was complete (ca. 4 hr). The solution was filtered through celite and concentrated to give a crude product as a solid. The crude product was triturated with ether, and filtered. The filter cake was dried *in vacuo* to yield cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (6.1 g, 95% yield). ^{1}H NMR (dmso-d6): 10.86 (1H, br. s), 10.34 (1H, br. s), 10.04 (1H, br. s), 8.46 (1H, s), 7.84-7.80 (1H, dd), 7.66-7.62 (2H, m), 7.55 (1H, s), 7.47-7.45 (1H, m), 7.41-7.37 (1H, m), 7.24 (1H, s), 7.18-7.13 (2H, t), 3.98 (3H, s), 1.46 (4H, s).

Example 23



[0184] N-[3-Fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a mixture of cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (1.5 g, 2.96 mmol), 4-(3-hydroxypropyl)morpholine (0.623 mL, 4.5 mmol), triphenylphosphine (1.18 g, 4.5 mmol), and dichloromethane (50 mL) was added diisopropyl azodicarboxylate (0.886 mL, 4.5 mmol). The mixture was stirred at room temperature for 16 h, monitored by LCMS. After removal of solvent, the crude mixture was separated by flash column chromatography (silica), eluting with 5% methanol in dichloromethane to give N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (890 mg, 47% yield). 1HNMR (400MHz, DMSO-d6): d 10.36 (br s, 1H), 10.05 (br s, 1H), 8.55 (s, 1H), 7.83 (m, 1H), 7.64 (m, 2H), 7.57 (s, 1H), 7.44 (m, 3H), 7.18 (t, 2H), 4.27 (m, 2H), 3.99 (s, 3H), 3.61 (m, 6H), 2.40 (m, 4H), 2.01 (m, 2H), 1.47 (m, 4H). LC/MS Calcd for $[M+H]^+$ 634.2, found 634.3.

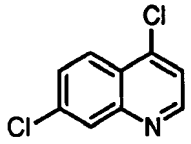
Example 24



[0185] N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. To a solution of cyclopropane-1,1-dicarboxylic acid (4-

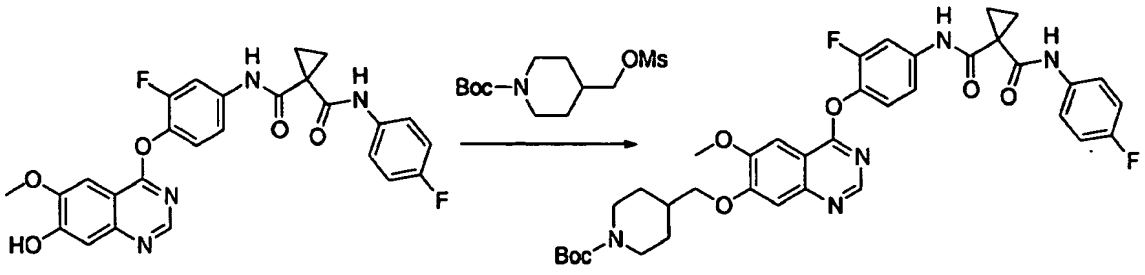
fluoro-phenyl)-amide (4-hydroxy-phenyl)-amide (6.98 g, 22.2 mmol) in anhydrous 2,6-lutidine (50 mL) was added trifluoromethanesulfonic acid 6, 7-dimethoxy-quinolin-4-yl ester (5 g, 14.8 mmol). The reaction mixture was heated at 165°C in a sealed pressure tube with stirring for 18 h. The reaction mixture was concentrated on high vacuum to completely remove lutidine. The resulting solid material was dissolved in DCM (250 mL), and washed several times with 1 N sodium hydroxide to remove the excess phenol. The crude mixture was loaded on a silica gel flash column and eluted with 75% EtOAc-hexanes, affording N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (3.2 g, 44%). ^{1}H NMR (400 MHz, d_6-DMSO): δ 10.2 (s, 1H), 10.05 (s, 1H), 8.4 (s, 1H), 7.8 (m, 2H), 7.65 (m, 2H), 7.5 (s, 1H), 7.35 (s, 1H), 7.25 (m, 2H), 7.15(m, 2H), 6.4 (s, 1H), 4.0 (d, 6H), 1.5 (s, 4H). LC/MS: M+H= 502.

Example 25



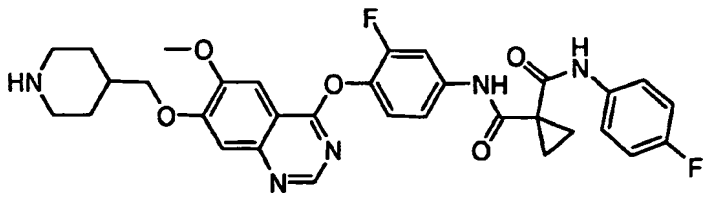
[0186] 4,7-Dichloroquinoline. Phosphorus oxychloride (4mL, 429 mmol) was added to 7-chloro-4-hydroxyquinoline 2.86g, 15.9mmol) in a round bottom flask equipped with a reflux condenser. The mixture was heated to reflux for 2h, then allowed to cool to room temperature. The solution was concentrated *in vacuo* to a thick oil, then dumped over cracked ice. The resulting solution was neutralized with saturated $NaHCO_3$ (aq). The slurry was filtered and washed with water. The solids were dried under vacuum, afforded 4,7-dichloroquinoline as a white solid (2.79g, 88.5% yield).

Example 26



[0187] **4-[4-(2-Fluoro-4-{[1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarbonyl]-amino}-phenoxy)-6-methoxy-quinazolin-7-yloxymethyl]-piperidine-1-carboxylic acid tert-butyl ester.** Cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(7-hydroxy-6-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (325 mg, 0.64 mmol), 4-methanesulfonyloxymethyl-piperidine-1-carboxylic acid tert-butyl ester (193 mg, 0.66 mmol), K_2CO_3 (181 mg, 1.31 mmol) were combined in DMF (5 ml) and heated to 80°C overnight. The reaction was not complete and more 4-methanesulfonyloxymethyl-piperidine-1-carboxylic acid tert-butyl ester (90 mg, 0.31 mmol) and K_2CO_3 (90 mg, 0.65 mmol) were added and heating at 80°C continued for another night. The reaction mixture was allowed to cool to room temperature, then diluted with EtOAc and washed with H_2O (3x), sat'd NaCl (1x), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting crude material was purified by flash chromatography (1:1 hexanes:EtOAc, followed by 1:3 hexanes:EtOAc) to give 4-[4-(2-fluoro-4-{[1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarbonyl]-amino}-phenoxy)-6-methoxy-quinazolin-7-yloxymethyl]-piperidine-1-carboxylic acid tert-butyl ester (273 mg, 60%). LC/MS Calcd for $[M+H]^+$ 704.3, found 704.4.

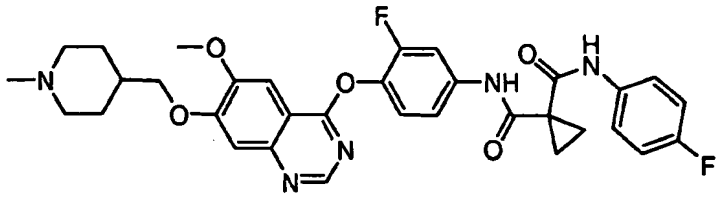
Example 27



[0188] **Cyclopropane-1,1-dicarboxylic acid {3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-amide (4-fluoro-phenyl)-amide, TFA salt.** 4-[4-

(2-Fluoro-4-{[1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarbonyl]-amino}-phenoxy)-6-methoxy-quinazolin-7-yloxymethyl]-piperidine-1-carboxylic acid tert-butyl ester (273 mg, 0.39 mmol) was dissolved in CH_2Cl_2 (8 ml) to which was added TFA (8 ml) and the mixture stirred at room temperature for 1hr. The reaction mixture was concentrated *in vacuo* and the resulting oil triturated with Et_2O. The resulting solids were filtered, washed with Et_2O and dried under high vacuum to give cyclopropane-1,1-dicarboxylic acid {3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-amide (4-fluoro-phenyl)-amide, TFA salt (222 mg, 80%). LC/MS Calcd for $[M+H]^+$ 604.2, found 604.3.

Example 28



[0189] **N-{3-Fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.** Cyclopropane-1,1-dicarboxylic acid {3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-amide (4-fluoro-phenyl)-amide, TFA salt (222 mg, 0.31 mmol), H_2O (3 ml), 37% formaldehyde in H_2O (0.18 ml) and acetic acid (27 drops) were combined in acetonitrile (9 ml) to which was slowly added triacetoxyborohydride (561 mg, 2.65 mmol). The mixture was stirred at room temperature for 1-2 hr, then diluted with 1N NaOH and H_2O and extracted with CH_2Cl_2 (3x). The combined CH_2Cl_2 extractions were washed with sat'd NaCl (1x), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was dissolved in a minimum of 1:1 dioxane:EtOAc to which was added 4M HCl in dioxane (1-2 ml). The resulting solids were filtered, washed with EtOAc and dried under high vacuum to give N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy] phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, HCl salt (167 mg, 83%). 1HNMR (400MHz, DMSO-d_6): δ 10.40 (s, 1H), 10.17 (br s, 1H) 10.07 (s, 1H), 8.61 (s, 1H), 7.85 (m, 1H), 7.65 (m, 2H), 7.48 (m, 2H), 7.42 (t, 1H), 7.16 (t, 2H), 4.12 (2, 2H), 4.00 (s, 3H), 3.46 (m, 2H), 2.99 (m, 2H), 2.73 (d, 3H), 2.13 (m, 1H), 2.01 (m, 2H), 1.63 (m, 2H), 1.47 (m, 4H). LC/MS Calcd for $[M+H]^+$ 618.2, found 618.3.

Synthesis of Bridged Bicyclics

[0190] The following describes synthesis of bridged bicyclics with appended leaving groups for use as, for example, alkylating agents. In the context of this invention, these alkylating agents are used, for example, to alkylate the quinazoline or quinolines on the 6- or 7-oxygens to make compounds of the invention. The invention is not limited to alkylation chemistry to append such bridged bicyclics, but rather the aforementioned description is meant only to be illustrative of an aspect of the invention.

Example 29

[0191] **1,4:3,6-dianhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-D-glucitol**: To a solution of 1,4:3,6-dianhydro-2-*O*-methyl-D-glucitol (1.19g, 7.4 mmol) in dichloromethane was added pyridine (1mL, 12.36 mmol) followed by methanesulfonyl chloride (0.69mL, 8.92 mmol) and the mixture was allowed to stir at room temperature over 12 hours. The solvent was removed and the amorphous residue was partitioned with ethyl acetate and 0.1M aqueous hydrochloric acid. The aqueous phase was extracted once with additional ethyl acetate and the combined organic layers were washed with saturated aqueous sodium chloride then dried over anhydrous magnesium sulfate. Filtration and concentration followed by drying *in vacuo* afforded 1,4:3,6-dianhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-D-glucitol (1.67g, 94% yield) as a colorless oil. GC/MS calculated for $C_8H_{14}SO_6$: 238 (M^+).

Example 30

[0192] **1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-D-fructose ethylene glycol acetal:** A solution of 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-D-fructose (2.00g, 8.06 mmol), ethylene glycol (5.00g, 80.6 mmol), and *p*-toluenesulfonic acid (1.53g, 8.06 mmol) in benzene (100mL) was refluxed for 90 min using a Dean-Stark Trap apparatus. The reaction mixture was diluted with ethyl acetate (100mL), washed with saturated aqueous sodium bicarbonate (2 x 50mL) then brine (50mL), and dried over anhydrous sodium sulfate. Filtration, concentration and column chromatography on silica (1:1 hexane/ethyl acetate) provided 1.44g (61% yield) of 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-D-fructose ethylene glycol acetal as a colorless solid. ^{1}H NMR (400 MHz; $CDCl_3$): 8.08 (m, 2H), 7.58 (m, 1H), 7.54 (m, 2H), 5.38 (dd, 1H), 4.97 (t, 1H), 4.21-4.02 (m, 7H), 3.86 (d, 1H), 3.75 (d, 1H).

Example 31

[0193] **1,4:3,6-dianhydro-D-fructose ethylene glycol acetal**: To a solution of 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-D-fructose ethylene glycol acetal (1.44g, 4.93 mmol) in methanol (40mL) was added 50% aqueous sodium hydroxide (0.38 g, 4.75 mmol) and the mixture was stirred at room temperature for 30 minutes. Neutralization with 1M HCl, followed by concentration and column chromatography on silica (1:2 hexane/ethyl acetate) provided 0.74g (80% yield) of 1,4:3,6-dianhydro-D-fructose ethylene glycol acetal as a colorless solid. ^{1}H NMR (400 MHz; $CDCl_3$): 4.60 (t, 1H), 4.32 (m, 1H), 4.14 (d, 1H), 4.05-3.98 (m, 5H), 3.82 (s, 2H), 3.62 (dd, 1H), 2.65 (d, 1H).

[0194] **1,4:3,6-dianhydro-5-*O*-(methylsulfonyl)-D-fructose ethylene glycol acetal**: To a solution of 1,4:3,6-dianhydro-D-fructose ethylene glycol acetal (0.74g, 3.93 mmol) and triethylamine (1.20g, 11.86 mmol) in dichloromethane (40mL) was added methanesulfonyl chloride (0.90g, 7.88 mmol) at 0°C under nitrogen. The solution was warmed to room temperature and stirred for 13 h. Dichloromethane (50mL) was added, and the organic layer was washed with saturated aqueous sodium bicarbonate (30mL), water (30mL), and brine (30mL) then dried over anhydrous sodium sulfate. Filtration and concentration provided 1.02g (97%) of 1,4:3,6-dianhydro-5-*O*-(methylsulfonyl)-D-fructose ethylene glycol acetal as a yellow oil. ^{1}H NMR (400 MHz; $CDCl_3$): 5.08 (m, 1H), 4.82 (t, 1H), 4.13 (dd, 1H), 4.04 (m, 4H), 3.93 (dd, 1H), 3.87 (d, 1H), 3.81 (d, 1H), 3.13 (s, 3H).

Example 32

[0195] **1,4:3,6-dianhydro-2-deoxy-2-methylidene-D-*arabino*-hexitol**: To a solution of 1,4:3,6-dianhydro-2-deoxy-2-methylidene-5-*O*-(phenylcarbonyl)-D-*arabino*-hexitol (329mg, 1.34 mmol) in methanol (10mL) was added 50% aqueous sodium hydroxide (95mg, 1.19 mmol) and the mixture was stirred at room temperature for 30 minutes. Neutralization with 4M hydrogen chloride in 1,4-dioxane followed by concentration and column chromatography on silica (1:1 hexane/ethyl acetate) provided 141mg (74%) of 1,4:3,6-dianhydro-2-deoxy-2-methylidene-D-*arabino*-hexitol as a colorless solid. ^{1}H NMR (400 MHz; $CDCl_3$): 5.37 (m, 1H), 5.20 (m, 1H), 4.80 (m, 1H), 4.54 (m, 2H), 4.43 (m, 1H), 4.26 (m, 1H), 3.95 (dd, 1H), 3.54 (dd, 1H), 2.70 (d, 1H).

[0196] **1,4:3,6-dianhydro-2-deoxy-2-methylidene-5-*O*-(methylsulfonyl)-D-*arabino*-hexitol**: To a solution of 1,4:3,6-dianhydro-2-deoxy-2-methylidene-D-*arabino*-hexitol (135mg, 0.95 mmol) and triethylamine (288mg, 2.85 mmol) in dichloromethane (10mL) was added methanesulfonyl chloride (222mg, 1.94 mmol) at 0°C under nitrogen. The solution was warmed to room temperature and stirred for 18 h. Dichloromethane (50mL) was added and the organic layer was washed with saturated aqueous sodium bicarbonate (2 x 25mL), water (25mL) and brine (25mL) then dried over anhydrous sodium sulfate. Filtration and concentration provided 213mg (72%) of 1,4:3,6-dianhydro-2-deoxy-2-methylidene-5-*O*-(methylsulfonyl)-D-*arabino*-hexitol as a yellow oil. ^{1}H NMR (400 MHz; $CDCl_3$): 5.40 (m, 1H), 5.23 (m, 1H), 5.04 (m, 1H), 4.85 (m, 1H), 4.73 (t, 1H), 4.58 (m, 1H), 4.41 (m, 1H), 4.08 (dd, 1H), 3.86 (dd, 1H), 3.14 (s, 3H).

Example 33

[0197] **1,4:3,6-dianhydro-2-deoxy-5-*O*-(phenylcarbonyl)-L-*arabino*-hex-1-enitol**: To a mixture of 1,4:3,6-dianhydro-5-*O*-(phenylcarbonyl)-(D)-glycitol (4.32g, 17.3 mmol), triethylamine (4.91 mL, 35.3 mmol) and 4-dimethylaminopyridine (0.63g, 5.2 mmol) in dichloromethane (50 mL) at -10 ° to -15° was added trifluromethanesulfonic anhydride (3.48mL, 20.7 mmol) dropwise over ten minutes and the resulting mixture was stirred at this temperature for 3 hours. The mixture was poured into 100 mL of ice-water and extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered then concentrated. The crude triflate was suspended in toluene (50 mL) followed by addition of 1,8-diazabicyclo[4,5,0]undec-7-ene (5.25 mL, 34.6 mmol) and the mixture was stirred at room temperature for 18 hours. The reaction mixture was poured into ice-water and partitioned then the aqueous portion was extracted with dichloromethane (3 x 50 mL). The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flashed chromatography (silica gel, 5-20% ethyl acetate-hexane) to give 1,4:3,6-dianhydro-2-deoxy-5-*O*-(phenylcarbonyl)-L-*arabino*-hex-1-enitol, as a white solid, 3.10g, 77% yield. ^{1}H NMR (400MHz; $CDCl_3$): 8.08-8.06 (m, 2H), 7.61-7.57 (m, 1H), 7.56-7.43 (m, 2H), 6.62-6.61 (d, 1H), 5.48-5.46 (m,1H), 5.32-5.26 (m,1H), 5.13-5.10 (m, 2H), 4.18-4.14 (tr,1H), 3.61-3.56 (tr, 1H).

Example 34

[0198] **Methyl 3,6-anhydro-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside**: To a solution of 1,4:3,6-dianhydro-2-deoxy-5-*O*-(phenylcarbonyl)-L-arabino-hex-1-enitol (1.00g, 4.3 mmol) in methanol (17 mL) at -4°C was added 3-chloroperoxybenzoic acid (85%, 1.35g, 8.6 mmol), and the resulting mixture was slowly warmed to room temperature and stirred for 18 hours. The reaction mixture was concentrated, diluted with dichloromethane (50 mL), washed with saturated aqueous sodium bicarbonate solution, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (silica gel, 25-60% ethyl acetate-hexane) to give methyl 3,6-anhydro-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside as a white solid, 1.03g, 83% yield. ^{1}H NMR (400MHz; $CDCl_3$): 8.11-8.08 (d, 2H), 7.61-7.56 (tr, 1H), 7.48-7.44 (m, 2H), 5.24-5.17 (m, 2H), 4.96 (s, 1H), 4.57-4.56 (d, 1H), 4.27 (s, 1H), 4.22-4.18 (dd, 1H), 4.08-4.04 (dd, 1H) 3.36 (s, 3H).

[0199] **Methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside**: A mixture of methyl 3,6-anhydro-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside (1.03g, 3.7 mmol), silver (I) oxide (0.85g, 3.7 mmol) and methyl iodide (0.34 mL, 5.5 mmol) in DMF (2 mL) was heated at 60°C for 1 hour. After cooling to room temperature the reaction mixture was diluted with ethyl acetate (50 mL), filtered over celite, adsorbed on silica gel (10g) and purified by flash chromatography (silica gel, 5-30% ethyl acetate-hexane) to give methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside as a colorless oil, 0.82g, 76% yield. ^{1}H NMR (400MHz; $CDCl_3$): 8.11-8.09 (d, 2H), 7.60-7.56 (m, 1H), 7.46-7.44 (m, 2H), 5.24-5.20 (m, 1H), 5.18-5.09 (tr, 1H), 4.99 (s, 1H), 4.61-4.60 (d, 1H), 4.21-4.17 (tr, 1H), 4.08-4.03 (tr, 1H), 3.81 (s, 1H), 3.40 (s, 3H), 3.57 (s, 3H).

[0200] **Methyl 3,6-anhydro-2-*O*-methyl-α-D-idofuranoside**: A solution of methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-β-L-glucofuranoside (820mg, 3.1mmol) and 50% sodium hydroxide (248 mg, 3.1 mmol) in methanol (10mL) was stirred at room temperature for 30 minutes. The material was adsorbed on silica gel (5g) and passed through a short column (15% ethyl acetate in hexanes to 5% methanol in ethyl acetate) to give methyl 3,6-anhydro-2-*O*-methyl-α-D-idofuranoside as a colorless oil, 420 mg, 85% yield. ^{1}H NMR (400MHz; $CDCl_3$): 5.04 (s, 1H), 5.84-5.81 (tr, 1H), 4.44-4.42 (tr, 1H), 4.25-4.19 (m, 1H), 3.85-3.75 (m, 1H), 3.49 (s, 3H), 3.43 (s, 3H), 2.75-2.72 (d, 1H).

[0201] **Methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-β-L-glucofuranoside**: Methyl 3,6-anhydro-2-*O*-methyl-α-D-idofuranoside (420 mg, 2.6 mmol) was dissolved in dichloromethane (10 mL) and pyridine (0.36 mL, 3.7 mmol) at 0°C. Methanesulfonyl chloride (0.14 mL, 3.1 mmol) was added and the resulting mixture was stirred at 0°C for 1 hour then at room temperature for 2 hours. The reaction mixture was washed with water and saturated aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, filtered and concentrated to give methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-β-L-glucofuranoside as a colorless oil, 669mg, 95% yield, which was used without further purification.

Example 35

[0202] **3,6-anhydro-5-*O*-(phenylcarbonyl)-α-L-glucofuranose**: A mixture of osmium tetroxide (4% in water, 0.25 mL, 0.03 mmol) and N-methylmorpholine (505 mg, 4.3 mmol) in 3 mL of 50% acetone in water was warmed to 60°C. A solution of 1,4:3,6-dianhydro-2-deoxy-5-*O*-(phenylcarbonyl)-L-*arabino*-hex-1-enitol (2.00g, 8.6 mmol) in 6 mL of 50% acetone in water was added over 3 hours. During this time an additional amount of N-methylmorpholine (1.01g, 8.6 mmol) was added in small portions periodically. Upon completion of the addition process the reaction was stirred for another hour and cooled to room temperature. The crude mixture was applied to a column of silica gel and flashed (0-6% methanol in 1:1 ethyl acetate:hexane) to give 3,6-anhydro-5-*O*-(phenylcarbonyl)-α-L-glucofuranose as a white solid, 1.5g, 65% yield. ^{1}H NMR (400MHz; DMSO-d_6): 8.01-7.95, (m, 2H), 7.68-7.66 (m, 1H), 7.57-7.53 (m, 2H), 5.18-5.11 (m, 2H), 4.85-4.81 (m, 1H, m), 4.37-4.35 (m, 1H), 4.05-3.96 (m, 2H), 3.85-3.83 (m, 1H).

[0203] **3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-α-L-glucofuranoside**: 3,6-Anhydro-5-*O*-(phenylcarbonyl)-α-L-glucofuranose (576 mg, 2.2 mmol) was added to a mixture of sodium hydride (60% oil dispersion, 346 mg, 8.7 mmol) and methyl iodide (0.54mL, 8.7 mmol) in 5 mL of DMF at 0°C and the resulting mixture was stirred for 1 hour. The reaction mixture was diluted with ethyl acetate and quenched with water (5 mL). The aqueous portion was extracted with ethyl acetate (3 x 5 mL). The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flashed chromatography (silica gel, 5-20% ethyl acetate in hexane) to give 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-α-L-glucofuranoside as a white solid,

270 mg, 42% yield. ^{1}H NMR (400MHz; $CDCl_3$): 8.09-8.07 (m, 2H), 7.61-7.57 (m, 1H), 7.48-7.27 (m, 2H), 5.25-5.22 (m, 1H), 5.07-5.06 (d, 1H), 4.94-4.91 (m, 1H), 4.73-4.71 (m, 1H), 4.20-4.16 (m, 1H), 3.96-3.94 (m, 1H), 3.85-3.83 (tr, 1H), 3.50 (s, 3H), 3.42 (s, 3H).

[0204] **Methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-α-L-glucofuranoside**: A solution of methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(phenylcarbonyl)-α-L-glucofuranoside (230mg, 0.92 mmol) and 50% sodium hydroxide (74 mg, 0.92 mmol) in methanol (5 mL) was stirred at room temperature for 30 minutes. The mixture was adsorbed on silica gel (2g) and passed through a short column (15% ethyl acetate in hexanes to 5% methanol in ethyl acetate) to afford a colorless oil which was employed directly in the next step, 140 mg, 0.72 mmol, 95% yield. The alcohol was dissolved in dichloromethane (5 mL) and pyridine (121 μL, 1.03 mmol) was added at 0°C. Methanesulfonyl chloride (27μL, 0.88 mmol) was added and the resulting mixture was stirred at 0°C for 1 hour then at room temperature for 2 hours. The reaction mixture was washed with water and saturated aqueous sodium bicarbonate solution, dried over sodium sulfate, filtered and concentrated to give methyl 3,6-anhydro-2-*O*-methyl-5-*O*-(methylsulfonyl)-α-L-glucofuranoside as a colorless oil, 190 mg, 96% yield.

Example 36

[0205] **3,6-Anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(phenylcarbonyl)-α-L-glucofuranose:** A mixture of 3,6-anhydro-5-*O*-(phenylcarbonyl)-α-L-glucofuranose (1.00g), 2,2-dimethoxy propane (0.63 mL), p-toluenesulfonic acid (20 mg) and benzene (10 mL) was heated at reflux for 3 hours. The reaction mixture was cooled then adsorbed on silica gel (10g) and purified by flash chromatography (silica gel, 5-35% ethyl acetate in hexanes) to give 3,6-anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(phenylcarbonyl)-α-L-glucofuranose as colorless oil, 0.85g, 74% yield. ^{1}H NMR (400MHz; $CDCl_3$): 8.08-8.06 (d, 2H), 7.59-7.56 (tr, 1H), 7.46-7.42 (m, 2H), 5.99-5.98 (d, 1H), 5.35-5.31 (tr, 1H), 5.10-5.08 (d, 1H), 4.66-4.65 (d, 1H), 4.61-4.60 (d, 1H), 4.20-4.16 (dd, 1H), 3.91-3.74 (tr, 1H,), 1.50 (s, 3H), 1.34 (s, 3H).

[0206] **3,6-Anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(methylsulfonyl)-α-L-glucofuranose**: A solution of 3,6-anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(phenylcarbonyl)-α-L-glucofuranose (850mg) and 50% sodium hydroxide (111 mg) in methanol (10mL) was stirred at room temperature for 30 minutes. The mixture was then adsorbed on silica gel (5g) and

passed through a short column (15% ethyl acetate in hexanes to 5% methanol in ethyl acetate) and the alcohol intermediate, 390 mg, 70% yield, was used immediately in the next step. The alcohol was dissolved in dichloromethane (10 mL) and pyridine (0.32 mL) at 0°C. Methanesulfonyl chloride (0.12 mL) was added and the resulting mixture was stirred at 0°C for 1 hour then at room temperature for 2 hours. The reaction mixture was washed with water and saturated aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, filtered and concentrated to give 3,6-anhydro-1,2-*O*-(1-methylethylidene)-5-*O*-(methylsulfonyl)-α-L-glucofuranose as a colorless oil, 485 mg, 90% yield, which was immediately employed in the next step.

Example 37

[0207] **(3*S*,8a*S*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine**: (*S*)-(+)-Prolinol (6.00 g, 59.3 mmol) was added to epichlorohydrin (47 mL, 600 mmol) at 0°C. The solution was stirred at 40°C for 0.5 h and then concentrated *in vacuo*. The residual oil was cooled in an ice bath and concentrated sulfuric acid (18 mL) was added dropwise with stirring. The mixture was heated at 170-180°C for 1.5 h, poured into ice (300 mL) and then basified with sodium carbonate to pH~8. The mixture was partitioned with ethyl acetate/hexanes and filtered. The filtrate was separated and the aqueous portion was extracted twice with ethyl acetate. The combined organic portion was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford oil that was purified by column chromatography (ethyl acetate for less polar product and then 30% methanol in ethyl acetate). (3*S*,8a*S*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine (less polar product) (1.87 g, 10.7 mmol, 18% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 4.06 (dd, 1H), 3.79-3.71 (m, 1H), 3.60-3.48 (m, 2H), 3.36 (dd, 1H), 3.15 (dd, 1H), 3.13-3.06 (m, 1H), 2.21-2.01 (m, 3H), 1.90-1.68 (m, 3H), 1.39-1.24 (m, 1H); MS (EI) for $C_8H_{14}NOCl$: 176 (MH^+). (3*R*,8a*S*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine (1.54 g, 8.77 mmol, 15% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 3.94-3.77 (m, 4H), 3.55 (dd, 1H), 3.02-2.93 (m, 2H), 2.45 (dd, 1H), 2.29-2.15 (m, 2H), 1.88-1.64 (m, 3H), 1.49-1.38 (m, 1H); MS (EI) for $C_8H_{14}NOCl$: 176 (MH^+).

[0208] Using the same or analogous synthetic techniques and/or substituting with alternative starting materials, the following were prepared:

[0209] **(3*R*,8a*R*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine**: ^{1}H NMR (400 MHz, $CDCl_3$): 4.05 (dd, 1H), 3.79-3.70 (m, 1H), 3.61-3.48 (m, 2H), 3.35 (dd, 1H), 3.15 (dd, 1H), 3.13-3.07 (m, 1H), 2.21-2.01 (m, 3H), 1.89-1.67 (m, 3H), 1.39-1.25 (m, 1H); MS (EI) for $C_8H_{14}NOCl$: 176 (MH^+).

[0210] **(3*S*,8a*R*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine**: ^{1}H NMR (400 MHz, $CDCl_3$): 3.93-3.77 (m, 4H), 3.55 (dd, 1H), 3.02-2.93 (m, 2H), 2.45 (dd, 1H), 2.30-2.15 (m, 2H), 1.88-1.64 (m, 3H), 1.49-1.37 (m, 1H); MS (EI) for $C_8H_{14}NOCl$: 176 (MH^+).

Example 38

[0211] **(3*S*,8a*S*)-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl acetate**: (3*S*,8a*S*)-3-(Chloromethyl)hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine (2.30 g, 13.1 mmol) and potassium acetate (12.8 g, 131 mmol) were stirred in dimethylformamide (25 mL) at 140°C for 20 h. The mixture was partitioned between ethyl acetate and water. The organic portion was washed twice with water, then with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford (3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl acetate as a brown oil (2.53 g, 12.7 mmol, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 4.14-4.02 (m, 3H), 3.81-3.72 (m, 1H), 3.37-3.31 (m, 1H), 3.09 (dt, 1H), 3.00 (dd, 1H), 2.21-2.00 (m, 3H), 2.10 (s, 3H), 1.90-1.67 (m, 3H), 1.39-1.24 (m, 1H); MS (EI) for $C_{10}H_{17}NO_3$: 200 (MH^+).

[0212] **(3*S*,8a*S*)-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethanol**: (3*S*,8a*S*)-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl acetate (2.36 g, 11.9 mmol) was treated with sodium methoxide (25 wt% solution in methanol; 2.7 mL) for 0.5 h. The mixture was cooled in an ice bath and a solution of 4M HCl in 1,4-dioxane (3 mL, 12.0 mmol) was added slowly. The mixture was stirred at room temperature for 5 minutes and then was concentrated *in vacuo* to afford a suspension which was diluted with dichloromethane, filtered and the filtrate was concentrated *in vacuo* to afford (3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethanol as a brown oil (1.93 g, >100% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 4.05 (dd, 1H), 3.73-3.65 (m, 2H), 3.62-3.56 (m, 1H), 3.39-3.34 (m, 1H), 3.10 (dt,

1H), 3.00-2.95 (m, 1H), 2.24-1.98 (m, 4H), 1.97-1.70 (m, 3H), 1.44-1.28 (m, 1H); MS (EI) for $C_8H_{15}NO_2$: 158 (MH^+).

[0213] **(3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl methanesulfonate**: (3*S*,8a*S*)-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethanol (1.00 g, 6.37 mmol) was dissolved in dichloromethane (10 mL) and triethylamine (2.4 mL, 17.3 mmol) was added at 0°C followed by dropwise addition of methanesulfonyl chloride (0.93 mL, 12.0 mmol). The solution was warmed to room temperature and stirred for 1.25 h and then was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic portion was washed with saturated sodium bicarbonate solution. The combined aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford (3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3-ylmethyl methanesulfonate as an orange-brown oil (1.20 g, 5.1 mmol, 80% yield). MS (EI) for $C_9H_{17}NO_4S$: 236 (MH^+).

Example 39

[0214] **Octahydro-2*H*-quinolizin-3-ylmethanol**: Ethyl octahydro-2*H*-quinolizine-3-carboxylate (2.35 g, 11.1 mmol) was added dropwise to a stirred suspension of lithium aluminum hydride (1 M solution in tetrahydrofuran, 33 mL, 33 mmol) in tetrahydrofuran (50 mL) at 0°C. The reaction was stirred at room temperature for 3 h. The mixture was cooled in an ice bath and ethyl acetate (6 mL) was added slowly, followed by water (1.25 mL), 15% aqueous sodium hydroxide solution (5 mL) and water (1.25 mL). The mixture was filtered through a pad of celite and washed with ether. The filtrate was concentrated *in vacuo* and dried rigorously to afford octahydro-2*H*-quinolizin-3-ylmethanol as a yellow oil (1.66 g, 9.82 mmol, 88% yield). MS (EI) for $C_{10}H_{19}NO$: 170 (MH^+).

[0215] **Octahydro-2*H*-quinolizin-3-ylmethyl methanesulfonate**: Octahydro-2*H*-quinolizin-3-ylmethanol (600 mg, 3.55 mmol) was dissolved in dichloromethane (8 mL) and triethylamine (1.5 mL, 10.8 mmol) was added at 0°C followed by dropwise addition of methanesulfonyl chloride (0.56 mL, 7.16 mmol). The solution was warmed to room temperature and stirred for 1.25 h and then was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The aqueous

portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford octahydro-2*H*-quinolizin-3-ylmethyl methanesulfonate as an orange oil (796 mg, 3.22 mmol, 91% yield). MS (EI) for $C_{11}H_{21}NO_3S$: 248 (MH^+).

Example 40

[0216] **(3*S*,8a*S*)-3-(Hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one**: A solution of methyl 1-[(2*S*)-3-hydroxy-2-({[(phenylmethyl)oxy]carbonyl}amino)propyl]-L-prolinate (3.50 g, 10.4 mmol) in methanol was added to 5% palladium on carbon (50 wt.% in water) in methanol and treated with hydrogen at 40 psi for 1 h. The mixture was filtered and the filtrate was brought to reflux briefly and then cooled and concentrated *in vacuo* to afford (3*S*,8a*S*)-3-(hydroxymethyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one as a colorless solid (1.50 g, 8.83 mmol, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 7.28-7.22 (m, 1H), 3.83-3.75 (m, 1H), 3.69 (dd, 1H), 3.56 (dd, 1H), 3.31 (t, 1H), 3.08 (dd, 1H), 2.92 (dt, 1H), 2.76-2.70 (m, 1H), 2.66 (dd, 1H), 2.28-2.16 (m, 1H), 2.02-1.73 (m, 3H); MS (EI) for $C_8H_{14}N_2O_2$: 171 (MH^+).

[0217] **(3*S*,8a*S*)-3-({[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}methyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one**: To a solution of (3*S*,8a*S*)-3-(hydroxymethyl) hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (1.49 g, 8.82 mmol) in dimethylformamide (20 mL) was added triethylamine (2.45 mL, 17.6 mmol) and 4-dimethylaminopyridine (90 mg, 0.882 mmol). The solution was cooled in an ice bath and *tert*-butyldimethylsilyl chloride (2.66 g, 17.6 mmol) was added. The mixture was warmed to room temperature and stirred for 14 h. The mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and water. The aqueous portion was extracted twice with ethyl acetate. The combined organic portion was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a pale brown solid which was triturated with ethyl acetate to afford (3*S*,8a*S*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one as an off-white solid (1.74 g, 5.84 mmol, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 6.09-5.90 (m, 1H), 3.86-3.76 (m, 1H), 3.63 (dd, 1H), 3.44 (dd, 1H), 3.25 (t, 1H), 3.10 (ddd, 1H), 2.98-2.90 (m, 1H), 2.68-2.60 (m, 1H), 2.52 (dd, 1H), 2.28-2.18 (m, 1H), 2.06-1.95 (m, 1H), 1.93-1.74 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H); MS (EI) for $C_{14}H_{28}N_2O_2Si$: 285 (MH^+).

[0218] **(3*S*,8a*S*)-3-({[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}methyl)-2-methylhexahydro pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one:** (3*S*,8a*S*)-3-({[(1,1-Dimethylethyl)(dimethyl)silyl]oxy} methyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (1.51g, 5.32mmol) in dimethylformamide (8 mL) was added to an ice-cooled suspension of sodium hydride (60 wt.% dispersion in oil; 213 mg, 5.32 mmol) in dimethylformamide (8 mL). The mixture was stirred at 0°C for 0.25 h and then iodomethane (0.332 mL, 5.32 mmol) was added dropwise. The mixture was stirred at room temperature for 0.5 h and then was stirred at 70°C for 2 h. The mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and water. The aqueous portion was extracted with ethyl acetate. The combined organic portion was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford (3*S*,8a*S*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)-2-methylhexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one as a yellow oil (1.552 g, 5.21 mmol) which was dissolved in tetrahydrofuran (20 mL) and treated with tetrabutylammonium fluoride (1.0M solution in tetrahydrofuran; 10.4 mL, 10.4 mmol) for 2 h at room temperature. The mixture was concentrated *in vacuo* and purified by column chromatography (10% methanol in dichloromethane) to afford (3*S*,8a*S*)-3-(hydroxymethyl)-2-methylhexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one as a yellow oil (496mg, 2.70mmol, 51% yield from (3*S*,8a*S*)-3-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy} methyl)hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one). ^{1}H NMR (400 MHz, $CDCl_3$): 3.98-3.93 (m, 1H), 3.86 (dd, 1H), 3.61-3.55 (m, 1H), 3.29-3.25 (m, 1H), 3.09-3.03 (m, 1H), 3.03-2.97 (m, 1H), 3.02 (s, 3H), 2.93 (dd, 1H), 2.87-2.79 (m, 1H), 2.32-2.21 (m, 1H), 2.00-1.86 (m, 2H), 1.83-1.64 (m, 1H); MS (EI) for $C_9H_{16}N_2O_2$: 185 (MH^+).

Example 41

[0219] **1,2-Dideoxy-1-[(2*S*)-2-(methoxycarbonyl)-1-pyrrolidinyl]-2-[[(phenylmethoxy) carbonyl]amino]-D-*glycero*-hexitol:** To a solution of 2-deoxy-2-{[(phenylmethyloxy) carbonyl]amino}-D-glycero-hexopyranose (5.0 g, 0.016 mol) in methanol (500 mL) was added L-proline methyl ester hydrochloride (2.8 g, 0.022 mol) and sodium cyanoborohydride (3.4 g, 0.054 mol). The solution was heated to 64 °C for 14 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* to afford 1,2-dideoxy-1-[(2*S*)-2-(methoxycarbonyl)-1-pyrrolidinyl]-2-[[(phenylmethoxy)carbonyl]amino]-D-*glycero*-hexitol (6.81 g, 100%) as a clear and colorless oil. MS (EI) for $C_{20}H_{31}N_2O_8$: 427 (MH^+).

Example 42

[0220] Methyl 1-[(2*S*)-3-hydroxy-2-({[(phenylmethyl)oxy]carbonyl}amino)propyl]-L-prolinate: 1,2-dideoxy-1-[(2*S*)-2-(methoxycarbonyl)-1-pyrrolidinyl]-2-[[(phenylmethoxy) carbonyl]amino]-D-*glycero*-hexitol (6.81 g, 0.016 mol) was taken into water (100 mL) and the resulting solution was cooled to 0°C. Sodium periodiate (14.8 g, 0.069 mol) dissolved in water was added dropwise and the resulting mixture was stirred at 0°C for 2 h. The reaction mixture was partitioned with dichloromethane (3x100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was taken up in methanol (200 mL) and the resulting solution was cooled to 0°C. Sodium borohydride (1.98 g, 0.052 mol) was added and the reaction mixture was stirred for 1 h at 0°C. The reaction mixture was concentrated *in vacuo* and partitioned with dichloromethane and saturated aqueous ammonium chloride. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude product was purified by column chromatography (5% methanol in dichloromethane) to yield methyl 1-[(2*S*)-3-hydroxy-2-({[(phenylmethyl)oxy]carbonyl}amino)propyl]-L-prolinate (4.9 g, 92%) as a white solid. MS (EI) for $C_{17}H_{25}N_2O_5$: 337 (MH^+).

[0221] Methyl 1-[(2*S*)-3-[(methylsulfonyl)oxy]-2-({[(phenylmethyl)oxy]carbonyl}amino) propyl]-L-prolinate: Methyl 1-[(2*S*)-3-hydroxy-2-({[(phenylmethyl)oxy]carbonyl}amino) propyl]-L-prolinate (200 mg, 0.594 mmol) was dissolved in dichloromethane (5 mL) followed by the addition of 4-(dimethylamino)pyridine (3.6 mg, 0.039 mmol) and triethylamine (0.125 mL, 0.891 mmol) and the resulting mixture was cooled to 0 °C. Methanesulfonyl chloride (0.060 mL, 0.773 mmol) was added dropwise and the reaction mixture was stirred for 1 h at 0°C. The mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford methyl 1-[(2*S*)-3-[(methylsulfonyl)oxy]-2-({[(phenylmethyl)oxy]carbonyl}amino)propyl]-L-prolinate (246 mg, 100%) as a clear and colorless oil. MS (EI) for $C_{18}H_{27}N_2O_7S$: 415 (MH^+).

Example 43

[0222] **1,1-Dimethylethyl (3a*R*,6a*S*)-5-(hydroxymethyl)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate**: Under a nitrogen atmosphere, borane tetrahydrofuran complex (1M in THF, 42 mL, 41.9 mmol) was diluted with tetrahydrofuran (42 mL) and cooled with an ice bath. Neat 2,3-dimethylbut-2-ene (5.0 mL, 41.9 mmol) was added in portions over 0.25 h and the solution was stirred at 0°C for 3 h. A solution of 1,1-dimethylethyl (3a*R*,6a*S*)-5-methylidenehexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate (1.98 g, 8.88 mmol) in tetrahydrofuran (10 mL) was added slowly, and the solution was warmed to room temperature and stirred 12 h. After cooling to 0°C, 10% aqueous sodium hydroxide (17 mL, 41.7 mmol) was added slowly, followed by 30% aqueous hydrogen peroxide (13 mL, 128 mmol) and the solution was warmed to room temperature. The solvent was removed *in vacuo* and the solution was partitioned between water and diethyl ether. The layers were separated and the aqueous layer was further extracted (3 x 50 mL diethyl ether). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to provide 2.04 (95%) of 1,1-dimethylethyl (3a*R*,6a*S*)-5-(hydroxymethyl)hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate, which was used without purification. ^{1}H NMR (400 MHz, $CDCl_3$): 8.50 (broad s, 1H), 3.66-3.46 (m, 3H), 3.20-3.00 (m, 2H), 2.70-2.59 (m, 2H), 2.37-2.18 (m, 1H), 2.04 (m, 1H), 1.84 (broad s, 1H), 1.70-1.55 (m, 1H), 1.46 (s, 9H), 1.17 (m, 1H), 0.93 (m, 1H).

[0223] **1,1-Dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]methyl}hexahydrocyclopenta [*c*]pyrrole-2(1*H*)-carboxylate**: Methanesulfonyl chloride (0.2mL, 2.48mmol), was added dropwise to a solution of 1,1-dimethylethyl (3a*R*,6a*S*)-5-(hydroxymethyl)hexahydro cyclopenta[*c*] pyrrole-2(1*H*)-carboxylate (0.40 g, 1.65 mmol) and triethylamine (0.69 mL, 4.95 mmol) in 20 mL dichloromethane at 0°C and the reaction mixture was stirred for 1 h at room temperature. The solvent was evaporated, the resulting crude mixture was diluted with 100 mL ethyl acetate and washed with water (30 mL), 1M aqueous sodium hydroxide, brine, 1M aqueous hydrochloric acid and brine again. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting 1,1-dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]methyl}hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate was used without further purification. MS (EI) for $C_{14}H_{25}NO_5S$: 320 (MH^+), 264 (M-tBu).

Example 44

[0224] **1,1-Dimethylethyl (3a*R*,6a*S*)-5-(hydroxy)-hexahydrocyclopenta[*c*] pyrrole-2(1*H*)-carboxylate**: Sodium borohydride (0.15 g, 4.00 mmol), was added to a solution of 1,1-dimethylethyl (3a*R*,6a*S*)-5-oxo-hexahydrocyclopenta[*c*] pyrrole-2(1*H*)-carboxylate (0.45 g, 2.00 mmol) in 10 mL methanol at 0°C and the reaction mixture was stirred for 1 h at this temperature. The solvent was evaporated, the crude mixture was diluted with 100 mL ethyl acetate and washed with water (30 mL), 1M aqueous hydrochloric acid and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give 1,1-dimethylethyl (3a*R*,6a*S*)-5-(hydroxy)-hexahydrocyclopenta[*c*] pyrrole-2(1*H*)-carboxylate (0.44g, 98%). ^{1}H NMR (400 MHz, d_6-DMSO): 4.08 (m, 1H), 3.40 (m, 2H), 3.30 (m, 2H), 2.50 (m, 2H), 1.98 (m, 2H), 1.40 (s, 9H), 1.30 (m, 2H). MS (EI) for $C_{12}H_{21}NO_3$: 228 (MH^+).

[0225] **1,1-Dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]}hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate**: Methanesulfonyl chloride (0.18 mL, 2.33 mmol), was added dropwise to a solution of 1,1-dimethylethyl (3a*R*,6a*S*)-5-(hydroxy)-hexahydrocyclopenta[*c*] pyrrole-2(1*H*)-carboxylate (0.44 g, 1.94 mmol) and triethylamine (0.81 mL, 5.81 mmol) in 10 mL dichloromethane at 0°C and the reaction mixture was stirred for 1 h at room temperature. The solvent was evaporated, the resulting crude mixture was diluted with 100 mL ethyl acetate and washed with water (30 mL), brine, 1M aqueous hydrochloric acid and brine again. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude 1,1-dimethylethyl (3a*R*,6a*S*)-5-{[(methylsulfonyl)oxy]}hexahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate was used without further purification. MS (EI) for $C_{13}H_{23}NO_5S$: 306 (MH^+).

Example 45

[0226] **3-(Chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine**: A solution of (3*R*)-morpholin-3-ylmethanol (4.21 g, 36.0 mmol) in 2-(chloromethyl)oxirane (28.2 mL, 0.360 mol) was heated to 40°C for 3 h and then the solution was concentrated *in vacuo*. The intermediate was cooled in an ice bath and treated with 30.0 mL of concentrated sulfuric acid. The mixture was heated to 170°C for 2 h and then allowed to cool to room temperature. The mixture was poured into ice-water and solid sodium bicarbonate was carefully added until the

solution was basic. 10% methanol in ethyl acetate was added and the biphasic mixture was filtered. The layers were separated and the aqueous layer was extracted (3 x 100 mL 10% methanol in ethyl acetate). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (SiO_2, 2:5 hexanes:ethyl acetate) provided 3-(chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine 2.44g (35%) as two separated diastereomers. (3*R*,9a*S*)-3-(chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine: (0.886 g, 13% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 3.91 (m, 3H), 3.82 (m, 1H), 3.68 (dt, 1H), 3.61 (dd, 1H), 3.47 (dd, 1H), 3.35 (t, 1H), 3.19 (t, 1H), 2.80 (d, 1H), 2.54 (m, 2H), 2.40 (m, 2H); MS (EI) for $C_8H_{14}NO_2Cl$: 192 (MH^+). (3*S*,9a*S*)-3-(chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine: (1.55 g, 22% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 3.85 (m, 2H), 3.73 (m, 3H), 3.50 (m, 2H), 3.29 (t, 1H), 3.18 (t, 1H), 2.85 (dd, 1H), 2.64 (dd, 1H), 2.40 (m, 2H), 2.17 (t, 1H); MS (EI) for $C_8H_{14}NO_2Cl$: 192 (MH^+).

[0227] **Hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate**: A suspension of (3*R*,9a*S*)-3-(chloromethyl)hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazine (1.97 g, 10.3 mmol) and potassium acetate (10.1 g, 102 mmol) in DMF (20.0 mL) was stirred at 140°C for 16 h, and then at 150°C for another 12 h. The reaction mixture was partitioned between water (250 mL) and ethyl acetate (250 mL), the organic layer was washed with 5% lithium chloride (2 x 100 mL) and brine (100 mL) then dried over anhydrous sodium sulfate and concentrated *in vacuo*. Column chromatography (SiO_2, 1:1 hexane:ethyl acetate, then 100% ethyl acetate) afforded 0.92 g (42%) of hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate as a yellow oil. Distinct diastereomers as described above were converted in this step to give: (3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate: ^{1}H NMR (400 MHz, $CDCl_3$): 4.18 (dd, 1H), 4.00 (m, 1H), 3.80 (dd, 1H), 3.68 (dt, 1H), 3.60 (dd, 1H), 3.46 (m, 2H), 3.22 (t, 1H), 2.64 (dd, 1H), 2.53 (m, 2H), 2.43-2.35 (m, 2H), 2.10 (s, 3H), and (3*S*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate: ^{1}H NMR (400 MHz, $CDCl_3$): 4.09 (d, 2H), 3.90-3.82 (m, 2H), 3.75-3.64 (m, 3H), 3.27 (t, 1H), 3.18 (t, 1H), 2.69 (dd, 1H), 2.63 (m, 1H), 2.46-2.33 (m, 2H), 2.16 (t, 1H), 2.10 (s, 3H).

[0228] **(3*R*,9a*S*)-Hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl methanesulfonate**: To a solution of (3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl acetate (0.922 g, 4.28 mmol) in methanol (14.0 mL) was added 1.03 mL (4.50 mmol) of sodium methoxide (25% wt. in methanol) dropwise at room temperature. After 5 min., 1.6 mL (6.43 mmol) of 4.0M hydrogen chloride in dioxane was added and a pink

precipitate formed. The solution was concentrated *in vacuo* and the pink solid was taken up in 30.0 mL dichloromethane. This slurry was cooled in an ice bath and triethylamine (3.0 mL, 21.5 mmol) was added, followed by methanesulfonyl chloride (0.37 mL, 4.71 mmol). The resultant yellow solution was stirred for 30 minutes at room temperature. The mixture was then partitioned between dichloromethane and saturated aqueous sodium bicarbonate then the aqueous layer was extracted (3 x 50 mL dichloromethane). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to provide crude (3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-*c*][1,4]oxazin-3-ylmethyl methanesulfonate which was taken on to the following reaction without purification.

Example 46

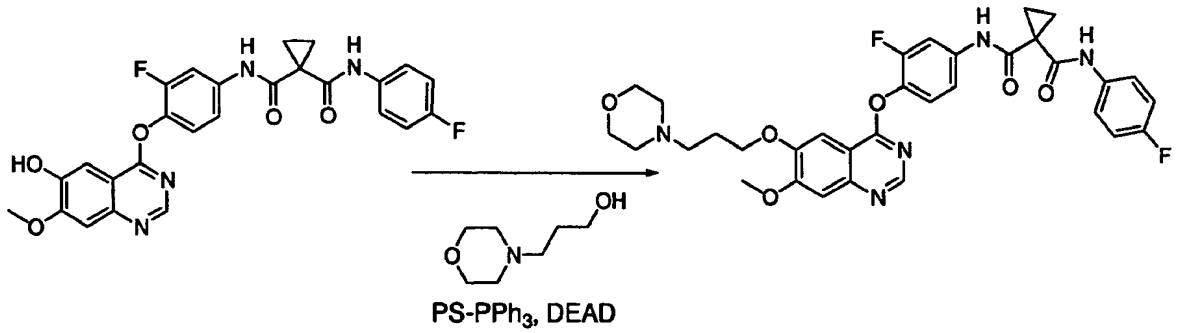
[0229] **(8a*R*)-6-(Chloromethyl)tetrahydro-1*H*-[1,3]thiazolo[4,3-*c*][1,4]oxazine**: A solution of (4*R*)-1,3-thiazolidin-4-ylmethanol (0.300 g, 2.52 mmol) in 2-(chloromethyl)oxirane (2.0 mL, 25.5 mmol) was heated under nitrogen to 40°C for 12 h. The solution was then cooled to room temperature and 2-(chloromethyl)oxirane was removed *in vacuo*. The crude intermediate was cooled in ice, and was taken up in 2.0 mL of concentrated sulfuric acid. The resulting mixture was heated to 200°C for 0.5 h then poured carefully onto wet ice, which was allowed to melt. The aqueous solution was carefully made basic using solid sodium bicarbonate and the resulting mixture was filtered using water and 10% methanol in ethyl acetate as eluent. The layers were separated and the aqueous layer was extracted with 10% methanol in ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give 11.6 mg (2.4% yield) of crude (8a*R*)-6-(chloromethyl)tetrahydro-1*H*-[1,3]thiazolo[4,3-*c*][1,4]oxazine as a mixture of diastereomers which was directly taken on to the next step.

Example 47

[0230] **1,1-Dimethylethyl (3-*endo*)-3-{2-[(methylsulfonyl)oxy]ethyl}-8-azabicyclo[3.2.1] octane-8-carboxylate**: To a solution of 1,1-dimethylethyl (3-*endo*)-3-(2-hydroxyethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (30.3 mg, 1.19 mmol) in dichloromethane (4.0 mL),

was added triethylamine (0.5 mL, 3.56 mmol) and the solution was cooled to 0°C under nitrogen. Methanesulfonyl chloride (0.11 mL, 1.42 mmol) was added slowly and mixture was allowed to warm to room temperature and stirred for 1h. The reaction mixture was partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane (2 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to provide 35.1 mg (89%) of 1,1-dimethylethyl (3-*endo*)-3-{2-[(methylsulfonyl)oxy]ethyl}-8-azabicyclo[3.2.1]octane-8-carboxylate, which was carried forward for alkylation without purification.

Example 48



[0231] **N-[3-Fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.** Crude cyclopropane-1,1-dicarboxylic acid [3-fluoro-4-(6-hydroxy-7-methoxy-quinazolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (333mg, 0.66mmol), PS-PPh_3 resin, (loading = 2.33mmol/g, 797mg, 1.86mmol), 3-morpholin-4-yl-propan-1-ol (0.26ml, 1.88mmol), and DEAD (0.31ml, 1.91mmol) were combined in CH_2Cl_2 (10ml) and stirred at room temperature for 1-2hrs. The reaction mixture was filtered and the resin thoroughly washed with CH_2Cl_2. The filtrate was concentrated *in vacuo* and the resulting residue was dissolved in EtOAc and washed with H_2O (4x) and sat'd NaCl (1x) and then extracted with 1N HCl (3x). The combined 1N HCl extractions were washed with EtOAc (2x). The acidic aqueous phase was then basified with 1N NaOH and extracted with EtOAc (3x). The combined EtOAc extractions were washed with H_2O (1x), sat'd NaCl (1x), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting residue was purified by preparative reverse phase HPLC (25mM

NH_4OAc/acetonitrile) and the pure fractions were lyophilized to give cyclopropane-1,1-dicarboxylic acid {3-fluoro-4-[7-methoxy-6-(3-morpholin-4-yl-propoxy)-quinazolin-4-yloxy]-phenyl}-amide (4-fluoro-phenyl)-amide (42.6mg, 10%). 1HNMR (400MHz, DMSO-d6): d 10.37 (br s, 1H), 10.05 (br s, 1H), 8.55 (s, 1H), 7.84 (m, 1H), 7.65 (m, 2H), 7.58 (s, 1H), 7.43 (m, 3H), 7.16 (t, 2H), 4.27 (m, 2H), 4.00 (s, 3H), 3.60 (m, 6H), 2.39 (m, 4H), 1.99 (m, 2H), 1.47 (m, 4H). LC/MS Calcd for $[M+H]^+$ 634.2, found 634.1.

[0232] Using the same or analogous synthetic techniques and/or substituting with alternative starting materials, the following were prepared:

[0233] **N-{3-fluoro-4-[(7-(methyloxy)-6-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide:** ^1H NMR (400MHz, $CDCl_3$): δ 9.67 (s, 1H), 8.59 (s, 1H), 8.43 (s, 1H), 7.75 (d, 1H), 7.52 (s, 1H), 7.46 (m, 2H), 7.31 (s, 1H), 7.20 (m, 2H), 7.06 (t, 2H), 4.04 (d, 2H), 4.03 (s, 3H), 2.98 (d, 2H), 2.34 (s, 3H), 2.12-2.1.95 (m, 5H), 1.76 (m, 2H), 1.64 (m, 2H), 1.57 (m, 2H).

Assays

[0234] Kinase assays were performed by measurement of incorporation of γ-^{33}P ATP into immobilized myelin basic protein (MBP). High binding white 384 well plates (Greiner) were coated with MBP (Sigma #M-1891) by incubation of 60ul/well of 20μg/ml MBP in Tris-buffered saline (TBS; 50mM Tris pH 8.0, 138mM NaCl, 2.7mM KCl) for 24 hours at 4° C. Plates were washed 3X with 100μl TBS. Kinase reactions were carried out in a total volume of 34μl in kinase buffer (5mM Hepes pH 7.6, 15mM NaCl, 0.01% bovine gamma globulin (Sigma #I-5506), 10mM $MgCl_2$, 1mM DTT, 0.02% TritonX-100). Compound dilutions were performed in DMSO and added to assay wells to a final DMSO concentration of 1%. Each data point was measured in duplicate, and at least two duplicate assays were performed for each individual compound determination. Enzyme was added to final concentrations of 10nM or 20nM, for example. A mixture of unlabeled ATP and γ-^{33}P ATP was added to start the reaction ($2x10^6$ cpm of γ-^{33}P ATP per well (3000Ci/mmole) and either 10μM or 30μM unlabeled ATP, typically. The reactions were carried out for 1 hour at room temperature with shaking. Plates were washed 7x with TBS, followed by the addition of 50μl/well scintillation

fluid (Wallac). Plates were read using a Wallac Trilux counter. This is only one format of such assays, various other formats are possible, as known to one skilled in the art.

[0235] The above assay procedure can be used to determine the IC_{50} for inhibition and/or the inhibition constant, K_i. The IC_{50} is defined as the concentration of compound required to reduce the enzyme activity by 50% under the conditions of the assay. Exemplary compositions have IC_{50}'s of, for example, less than about 100 μM, less than about 10 μM, less than about 1 μM, and further for example having IC_{50}'s of less than about 100 nM, and still further, for example, less than about 10 nM. The K_i for a compound may be determined from the IC_{50} based on three assumptions. First, only one compound molecule binds to the enzyme and there is no cooperativity. Second, the concentrations of active enzyme and the compound tested are known (i.e., there are no significant amounts of impurities or inactive forms in the preparations). Third, the enzymatic rate of the enzyme-inhibitor complex is zero. The rate (i.e., compound concentration) data are fitted to the equation:

$$V = V_{max} E_0 \left[I - \frac{(E_0 + I_0 + K_d) - \sqrt{(E_0 + I_0 + K_d)^2 - 4E_0 I_0}}{2E_0} \right]$$

where V is the observed rate, V_{max}, is the rate of the free enzyme, I_0 is the inhibitor concentration, E_0 is the enzyme concentration, and K_d is the dissociation constant of the enzyme-inhibitor complex.

Kinase specificity assays:

[0236] Kinase activity and compound inhibition are investigated using one or more of the three assay formats described below. The ATP concentrations for each assay are selected to be close to the Michaelis-Menten constant (K_M) for each individual kinase. Dose-response experiments are performed at 10 different inhibitor concentrations in a 384-well plate format. The data are fitted to the following four-parameter equation:

$$Y = Min + (Max - Min) / (1 + (X/IC_{50})^H)$$

where Y is the observed signal, X is the inhibitor concentration, Min is the background signal in the absence of enzyme (0% enzyme activity), Max is the signal in the absence of inhibitor

(100% enzyme activity), IC_{50} is the inhibitor concentration at 50% enzyme inhibition and H represents the empirical Hill's slope to measure the cooperativity. Typically H is close to unity.

c-Met Assay

[0237] c-Met biochemical activity was assessed using a Luciferase-Coupled Chemiluminescent Kinase assay (LCCA) format as described above. Again, kinase activity was measured as the percent ATP remaining following the kinase reaction. Remaining ATP was detected by luciferase-luciferin-coupled chemiluminescence. Specifically, the reaction was initiated by mixing test compounds, 1μM ATP, 1μM poly-EY and 10nM c-Met (baculovirus expressed human c-Met kinase domain P948-S1343) in a 20uL assay buffer (20mM Tris-HCL pH7.5, 10mM $MgCl_2$, 0.02% Triton X-100, 100mM DTT, 2mM $MnCl_2$). The mixture is incubated at ambient temperature for 2hours after which 20uL luciferase-luciferin mix is added and the chemiluminescent signal read using a Wallac Victor^2 reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5ug/mL oxalic acid (pH 7.8), 5 (or 50) mM DTT, 0.4% Triton X-100, 0.25 mg/mL coenzyme A, 63 uM AMP, 28 ug/mL luciferin and 40,000 units of light/mL luciferase.

KDR Assay

[0238] KDR biochemical activity was assessed using a Luciferase-Coupled Chemiluminescent Kinase assay (LCCA) format. Kinase activity was measured as the percent ATP remaining following the kinase reaction. Remaining ATP was detected by luciferase-luciferin-coupled chemiluminescence. Specifically, the reaction was initiated by mixing test compounds, 3 μM ATP, 1.6 μM poly-EY and 5 nM KDR (baculovirus expressed human KDR kinase domain D807-V1356) in a 20uL assay buffer (20mM Tris-HCL pH7.5, 10mM $MgCl_2$, 0.01% Triton X-100, 1mM DTT, 3mM $MnCl_2$). The mixture is incubated at ambient temperature for 4 hours after which 20uL luciferase-luciferin mix is added and the chemiluminescent signal read using a Wallac Victor^2 reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5ug/mL oxalic acid (pH 7.8), 5 (or 50) mM DTT, 0.4%

Triton X-100, 0.25 mg/mL coenzyme A, 63 uM AMP, 28 ug/mL luciferin and 40,000 units of light/mL luciferase.

flt-4 Assay

[0239] Biochemical activity for flt-4 was assessed using an Alphascreen Tyrosine Kinase protocol. AlphaScreen™ (Perkin Elmer) technology is a proximity assay employing microparticles. Singlet oxygen derived from a donor bead following laser excitation results in chemiluminescence when in proximity (100 Å) to an acceptor bead due to biomolecular interactions. For the Flt-4 assay, donor beads coated with streptavidin and acceptor beads coated with PY100 anti-phosphotyrosine antibody were used (Perkin Elmer). Biotinylated poly(Glu,Tyr) 4:1 (Perkin Elmer) was used as the substrate. Substrate phosphorylation was measured by addition of donor/acceptor beads by chemiluminescence following donor-acceptor bead complex formation. Test compounds, 5 μM ATP, 3 nM biotinylated poly(Glu, Tyr) and 1 nM Flt-4 (baculovirus expressed human Flt-4 kinase domain D725-R1298) were combined in a volume of 20 μL in a 384-well white, medium binding microtiter plate (Greiner). Reaction mixtures were incubated for 1 hr at ambient temperature. Reactions were quenched by addition of 10 uL of 15-30 mg/mL AlphaScreen bead suspension containing 75 mM Hepes, pH 7.4, 300 mM NaCl, 120 mM EDTA, 0.3% BSA and 0.03% Tween-20. After 2-16 hr incubation at ambient temperature plates were read using an AlphaQuest reader (Perkin Elmer). IC_{50} values correlate well with those determined by radiometric assays.

flt-3 Assay

[0240] Biochemical activity for flt-3 was assessed using a Luciferase-Coupled Chemiluminescent Kinase assay (LCCA) format. Kinase activity was measured as the percent ATP remaining following the kinase reaction. Remaining ATP was detected by luciferase-luciferin-coupled chemiluminescence. Specifically, the reaction was initiated by mixing test compounds, 5 μM ATP, 3 μM poly-EY and 5 nM Flt-3 (baculovirus expressed human Flt-3 kinase domain R571-S993) in a 20uL assay buffer (20mM Tris-HCL pH7.5, 10mM $MgCl_2$, 0.01% Triton X-100, 1mM DTT, 2mM $MnCl_2$). The mixture is incubated at ambient temperature for 3 hours after which 20uL luciferase-luciferin mix is added and the

chemiluminescent signal read using a Wallac Victor^2 reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5ug/mL oxalic acid (pH 7.8), 5 (or 50) mM DTT, 0.4% Triton X-100, 0.25 mg/mL coenzyme A, 63 uM AMP, 28 ug/mL luciferin and 40,000 units of light/mL luciferase.

c-Kit Assay

[0241] c-Kit biochemical activity was assessed using AlphaScreen ™ (Perkin Elmer) technology, described above. Test compounds, ATP, biotinylated poly(Glu, Tyr) and c-Kit kinase were combined in a volume of 20 μL in a 384-well white, medium binding microtiter plate (Greiner). Reaction mixtures were incubated for 1 hr at ambient temperature. Reactions were quenched by addition of 10 uL of 15-30 mg/mL AlphaScreen bead suspension containing 75 mM Hepes, pH 7.4, 300 mM NaCl, 120 mM EDTA, 0.3% BSA and 0.03% Tween-20. After 16 hr incubation at ambient temperature plates were read using an AlphaQuest reader (Perkin Elmer).

Structure Activity Relationships

[0242] Tables 2 and 3 show structure activity relationship data for selected compounds of the invention. Inhibition is indicated as IC_{50} with the following key: A = IC_{50} less than 50 nM, B = IC_{50} greater than 50 nM, but less than 500 nM, C = IC_{50} greater than 500 nM, but less than 5000 nM, and D = IC_{50} greater than 5,000 nM. Depending upon the functionality about the quinazoline or quinoline, exemplary compounds of the invention exhibit selectivity for any of c-Met, KDR, c-Kit, flt-3, and flt-4. Abbreviations for enzymes listed in Tables 2-3 are defined as follows: c-Met refers to hepatocyte growth factor receptor kinase; KDR refers to kinase insert domain receptor tyrosine kinase; flt-4, fms-like tyrosine kinase-4, representative of the FLK family of receptor tyrosine kinases; c-Kit, also called stem cell factor receptor or steel factor receptor; and flt-3, fms-like tyrosine kinase-3. Empty cells in the tables indicate lack of data only.

Table 2

Entry	Name	c-Met	KDR	flt-4
18	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(phenylmethyl)benzenesulfonamide	C		
19	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(2-phenylethyl)benzenesulfonamide	C		
20	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(2-phenylethyl)benzenesulfonamide	C		
21	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(3-phenylpropyl)benzenesulfonamide	C		
22	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)pyrrolidin-2-one	C		
23	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (phenylmethyl)carbamate	C		
24	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (2-phenylethyl)carbamate	C		
25	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(3-phenylpropyl)benzenesulfonamide	C		
26	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-phenylethanediamide	B	D	C
27	N-{[(3-fluoro-4-{[7-{[(2-methyloctahydrocyclopenta[c]pyrrol-5-yl)methyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}phenyl)amino]carbonothioyl}-2-phenylacetamide	A	A	A
28	N-[(Z)-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino](imino)methyl]-2-phenylacetamide	C		
29	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-[2-(phenyloxy)ethyl]benzenesulfonamide	C		
30	N,N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-bis-(3-phenylpropane-1-sulfonamide)	C		
31	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-phenylpropane-1-sulfonamide	C		
32	N2-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)sulfonyl]-N1-phenylglycinamide	C		
33	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-2-phenylacetamide	C		
34	N-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide	A	C	C

Table 2

Entry	Name	c-Met	KDR	flt-4
35	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-amine	C		
36	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-amine	C		
37	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-phenylacetamide	B	C	B
38	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-morpholin-4-ylethyl)ethanediamide	C		
39	benzyl-{[4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylcarbamoyl]-methyl}-carbamic acid tert-butyl ester	C		
40	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(phenylmethyl)glycinamide	B		
41	N2-acetyl-N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(phenylmethyl)glycinamide	C		
42	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-yl)-2-phenylacetamide	B		
43	benzyl-{[6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-ylcarbamoyl]-methyl}-carbamic acid tert-butyl ester	C		
44	N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-(phenylmethyl)glycinamide	C		
45	N2-acetyl-N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-(phenylmethyl)glycinamide	C		
46	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-3-phenylpropanamide	C		
47	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-4-phenylbutanamide	C		
48	N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-methyl-N2-(phenylmethyl)glycinamide	C		
49	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{2-[4-(methyloxy)phenyl]ethyl}ethanediamide	C		
50	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-(phenylmethyl)glycinamide	B	A	A
51	4-[(2-amino-1,3-benzothiazol-6-yl)oxy]-6,7-bis(methyloxy)-1-(2-oxo-2-phenylethyl)quinolinium	C		
52	N-{[(4-{[6,7-bis(methyloxy)quinolin-4-yl]amino}phenyl)amino]carbonothioyl}-2-phenylacetamide	A	B	A

Table 2

Entry	Name	c-Met	KDR	flt-4
53	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-3-phenylpropanamide	C		
54	N-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide	A	B	A
55	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2,3-dihydro-1H-inden-1-yl)ethanediamide	A	A	B
56	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2,3-dihydro-1H-inden-2-yl)ethanediamide	C		
57	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydronaphthalen-1-yl)ethanediamide	B	B	C
58	N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-(2-phenylethyl)-N-(phenylmethyl)sulfamide	C		
59	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(trifluoroacetyl)glycinamide	B	C	B
60	N-{[4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylcarbamoyl]-methyl}-benzamide	B	A	A
61	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N'-(4-fluorophenyl)propanediamide	A	B	B
62	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2S)-1,2,3,4-tetrahydronaphthalen-2-yl]ethanediamide	C		
63	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(4-methylphenyl)ethyl]ethanediamide	C		
64	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylpropyl)ethanediamide	B	A	B
65	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(4-chlorophenyl)ethyl]ethanediamide	B	C	C
66	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N,N'-bis(phenylmethyl)sulfamide	C		
67	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N,N'-bis(2-phenylethyl)sulfamide	C		
68	ethyl [(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino](oxo)acetate	C		
69	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl)ethanediamide	C		

Table 2

Entry	Name	c-Met	KDR	flt-4
70	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)propanediamide	A	B	C
71	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydronaphthalen-2-yl)ethanediamide	B	D	C
72	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(1-methylpyrrolidin-2-yl)ethyl]ethanediamide	C		
73	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(phenyloxy)ethyl]ethanediamide	B	B	C
74	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-hydroxy-1-(phenylmethyl)ethyl]urea	B		
75	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one	B	B	B
76	N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-methyl-N-(2-phenylethyl)ethanediamide	A	B	B
77	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{[3-(trifluoromethyl)phenyl]methyl}ethanediamide	B		
78	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{2-[3-(trifluoromethyl)phenyl]ethyl}ethanediamide	C		
79	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-3-oxo-4-phenylbutanamide	C		
80	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-2-[3-(trifluoromethyl)phenyl]acetamide	C		
81	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-[2-(phenyloxy)ethyl]-1,3-benzothiazol-2-amine	B		
82	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-(2-piperidin-1-ylethyl)-1,3-benzothiazol-2-amine	C		
83	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-methyl-N-(2-phenylethyl)-1,3-benzothiazol-2-amine	C		
84	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-(2-pyrrolidin-1-ylethyl)-1,3-benzothiazol-2-amine	C		
85	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-{[3-(trifluoromethyl)phenyl]methyl}-1,3-benzothiazol-2-amine	C		

Table 2

Entry	Name	c-Met	KDR	flt-4
86	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-{2-[3-(trifluoromethyl)phenyl]ethyl}-1,3-benzothiazol-2-amine	C		
87	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-[3-(trifluoromethyl)phenyl]propanediamide	C		
88	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3-(trifluoromethyl)phenyl]acetamide	B	B	
89	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-{[3-(trifluoromethyl)phenyl]methyl}glycinamide	B	A	A
90	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(2-phenylethyl)glycinamide	B		
91	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-{2-[3-(trifluoromethyl)phenyl]ethyl}glycinamide	B	B	A
92	benzyl-{[5-chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-ylcarbamoyl]-methyl}-carbamic acid tert-butyl ester	C		
93	N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N2-(phenylmethyl)glycinamide	C		
94	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3,5-bis(trifluoromethyl)phenyl]acetamide	C		
95	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[2-chloro-5-(trifluoromethyl)phenyl]acetamide	A	B	
96	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(2-phenylethyl)ethanediamide	A	A	
97	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)ethanediamide	C		
98	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]ethanediamide	B		
99	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-{[3-(trifluoromethyl)phenyl]methyl}glycinamide	C		

Table 2

Entry	Name	c-Met	KDR	flt-4
100	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-{2-[3-(trifluoromethyl)phenyl]ethyl}glycinamide	C		
101	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-(2-phenylethyl)glycinamide	C		
102	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-4-(phenylmethyl)imidazolidin-2-one	B	B	
103	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridazin-3-yl)-N'-(4-fluorophenyl)propanediamide	A	B	
104	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-chlorophenyl)propanediamide	B		
105	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(3-chlorophenyl)propanediamide	C		
106	N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N2-methyl-N2-(phenylmethyl)glycinamide	C		
107	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-chlorophenyl)propanediamide	B		
108	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(methyloxy)imino]propanamide	B		
109	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(ethyloxy)imino]propanamide	B		
110	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-{[(phenylmethyl)oxy]imino}propanamide	B		
111	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-1-(phenylmethyl)prolinamide	C		
112	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one	B		
113	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)imidazolidin-2-one	C		
114	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)-4,5-dihydro-1,3-oxazol-2-amine	C		
115	6,7-bis(methyloxy)-4-({4-[4-(phenylmethyl)piperazin-1-yl]phenyl}oxy)quinoline	C		
116	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)piperazin-2-one	C		

Table 2

Entry	Name	c-Met	KDR	flt-4
117	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-(phenylmethyl)alaninamide	C		
118	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-methyl-N2-(phenylmethyl)alaninamide	C	C	
119	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-(phenylmethyl)leucinamide	C		
120	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-methyl-N2-(phenylmethyl)leucinamide	C		
121	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-(phenylmethyl)valinamide	C		
122	4-(6,7-dimethoxy-quinolin-4-ylamino)-N-(3-phenyl-propyl)-benzamide	C		
123	4-benzyl-1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-tetrahydro-pyrimidin-2-one	C		
124	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	A	A	A
125	Cyclopropane-1,1-dicarboxylic acid [5-chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-amide (4-fluoro-phenyl)-amide	A	A	B
126	Cyclobutane-1,1-dicarboxylic acid [5-chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-amide (4-fluoro-phenyl)-amide	C		
127	2-(Benzyl-methyl-amino)-N-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-3-methyl-butyramide (note: Alphabetic order of prefixes ignored while selecting parent chain)	C	C	
128	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenyl]-2-phenoxyimino-propionamide	C	A	
129	2-Benzyloxyimino-N-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-2-phenyl-acetamide	B	C	
130	4-[4-(4-Benzyl-piperidin-1-yl)-phenoxy]-6,7-dimethoxy-quinoline	C		
131	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-oxalamide	B		
132	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-oxalamide	C		

Table 2

Entry	Name	c-Met	KDR	flt-4
133	4-(4-{3-Chloro-5-[2-(4-fluoro-phenylcarbamoyl)-acetylamino]-pyridin-2-yloxy}-6-methoxy-quinolin-7-yloxymethyl)-piperidine-1-carboxylic acid tert-butyl ester	B		
134	N-{5-Chloro-6-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	A	B	
135	N-{5-Chloro-6-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	A	B	
136	N-{4-[7-(3-Diethylamino-propoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide	A		
137	N-{3-Fluoro-4-[6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	A	A	
138	N-{3-Fluoro-4-[6-methoxy-7-(3-piperidin-1-yl-propoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	A	A	
139	N-{4-[7-(2-Diethylamino-ethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide	A	A	
140	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-methyl-N'-phenethyl-oxalamide	A	A	
141	N-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	A	A	
142	N-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	A	A	
143	2-(3,4-Dihydro-1H-isoquinolin-2-yl)-N-{3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-acetamide	A	A	
144	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-(3-phenyl-pyrrolidin-1-yl)-acetamide	A	A	
145	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-(2-phenyl-morpholin-4-yl)-acetamide	A	B	
146	N-(2-Dimethylamino-2-phenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide			

Table 2

Entry	Name	c-Met	KDR	flt-4
147	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-oxo-2-phenyl-ethyl)-oxalamide			
148	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-2,2-difluoro-N'-(4-fluoro-phenyl)-malonamide	C	C	
149	N-Benzyl-N'-{3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
150	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-fluoro-phenyl)-ethyl]-oxalamide	A	A	
151	N-[2-(3-Chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
152	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-methoxy-phenyl)-ethyl]-oxalamide	A	A	
153	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-3-yl-ethyl)-oxalamide	A	B	
154	N-Benzyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
155	N-[2-(2,5-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
156	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-trifluoromethyl-phenyl)-ethyl]-oxalamide	A	A	
157	N-[2-(2-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
158	N-[2-(2,4-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
159	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*S* -phenyl-2-p-tolyl-ethyl)-oxalamide	B	C	
160	N-[2-(4-Chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	

Table 2

Entry	Name	c-Met	KDR	flt-4
161	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamic acid	B	C	
162	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-fluoro-phenyl)-ethyl]-oxalamide	A	A	
163	N-[2-(2-Chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
164	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-methoxy-phenyl)-ethyl]-oxalamide	A	A	
165	N-(1,2-Diphenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
166	N-[2-(2,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
167	N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	B	
168	N-[2-(4-Ethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	B	
169	N-[2-(4-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	B	C	
170	N-[2-(4-Ethoxy-3-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	B	
171	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-phenoxy-phenyl)-ethyl]-oxalamide	B	C	
172	N-[2-(3-Ethoxy-4-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	C	
173	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-2-yl-ethyl)-oxalamide	A	A	

Table 2

Entry	Name	c-Met	KDR	flt-4
174	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-4-yl-ethyl)-oxalamide	A	A	
175	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-fluoro-phenyl)-ethyl]-oxalamide	A	A	
176	N-[2-(2-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
177	N-[2-(2-Chloro-6-fluoro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
178	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2*R*-phenyl-propyl)-oxalamide	A	A	
179	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-indan-1-yl-oxalamide	A	A	
180	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-isobutyl-oxalamide	A	B	
181	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-butyl)-oxalamide	A	B	
182	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2*R*-phenyl-propyl)-oxalamide	A	A	
183	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-phenyl-propyl)-oxalamide	A	A	
184	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-indan-2-yl-oxalamide	A	A	
185	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*R*-phenyl-ethyl)-oxalamide	A	B	
186	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*S*-phenyl-ethyl)-oxalamide	A	B	
187	N-[2-(3-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	

Table 2

Entry	Name	c-Met	KDR	flt-4
188	N-[2-(2,6-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
189	N-[2-(2,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
190	N-(2-Benzo[1,3]dioxol-5-yl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
191	Cyclopropane-1,1-dicarboxylic acid {5-chloro-6-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-pyridin-3-yl}-amide (4-fluoro-phenyl)-amide	A	A	
192	N-[2-(3-Bromo-4-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
193	N-[2-(3,5-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
194	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-o-tolyl-ethyl)-oxalamide	A	A	
195	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-m-tolyl-ethyl)-oxalamide	A	A	
196	N-[2-(3-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
197	N-[2-(3,4-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	B	
198	N-[2-(2,5-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
199	N-[2-(3-Chloro-4-propoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	B		
200	N-[2-(4-Butoxy-3-chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	B		

Table 2

Entry	Name	c-Met	KDR	flt-4
201	N-[2-(4-tert-Butyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	B		
202	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-sulfamoyl-phenyl)-ethyl]-oxalamide	A	B	
203	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-hydroxy-3-methoxy-phenyl)-ethyl]-oxalamide	A	B	
204	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-hydroxy-4-methoxy-phenyl)-ethyl]-oxalamide	A	B	
205	N-(2,4-Dichloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
206	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-fluoro-2-trifluoromethyl-benzyl)-oxalamide	B	A	
207	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-p-tolyl-ethyl)-oxalamide	A	B	
208	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-fluoro-4-trifluoromethyl-benzyl)-oxalamide	A	B	
209	N-(3-Chloro-4-fluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
210	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[1-(3-methoxy-phenyl)-ethyl]-oxalamide	A	B	
211	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-naphthalen-2-yl-ethyl)-oxalamide	A		
212	N-(4-Chloro-3-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
213	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-p-tolyl-ethyl)-oxalamide	A		

Table 2

Entry	Name	c-Met	KDR	flt-4
214	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(6-trifluoromethyl-pyridin-3-ylmethyl)-oxalamide	A	B	
215	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-methyl-benzyl)-oxalamide	A	A	
216	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-benzyl)-oxalamide			
217	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-fluoro-3-trifluoromethyl-benzyl)-oxalamide	A	A	
218	N-(3,5-Dichloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
219	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R,2,3,4-tetrahydro-naphthalen-1-yl)-oxalamide	A	D	
220	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1S,2,3,4-tetrahydro-naphthalen-1-yl)-oxalamide	A	A	
221	N-Cyclopentyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	B	
222	N-[1-(4-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	B	
223	N-(2-Fluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
224	N-[2-(3,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A		
225	N-(4-Fluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
226	N-(2,3-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
227	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-phenoxy-ethyl)-oxalamide	A	A	

Table 2

Entry	Name	c-Met	KDR	flt-4
228	N-(2,2-Diphenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	B	
229	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-methoxy-phenyl)-ethyl]-oxalamide	A	C	
230	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-phenyl-propyl)-oxalamide	A	A	
231	N-[2-(4-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	B	
232	N-{4-[7-(1-Ethyl-piperidin-4-ylmethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-2-oxo-2-(2-phenyl-morpholin-4-yl)-acetamide	A	B	
233	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-fluoro-5-trifluoromethyl-benzyl)-oxalamide	A	A	
234	N-(3,5-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
235	N-(2-Chloro-5-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
236	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-dimethylamino-2-phenyl-ethyl)-oxalamide	B	B	
237	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-methoxy-benzyl)-oxalamide	A	A	
238	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethyl-benzyl)-oxalamide	A	C	
239	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methoxy-benzyl)-oxalamide	A	A	
240	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-trifluoromethyl-benzyl)-oxalamide	A	A	

Table 2

Entry	Name	c-Met	KDR	flt-4
241	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-trifluoromethoxy-benzyl)-oxalamide	A	A	
242	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-methoxy-benzyl)-oxalamide	A	A	
243	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-trifluoromethyl-benzyl)-oxalamide	A	A	
244	N-(3-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
245	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-trifluoromethoxy-benzyl)-oxalamide	A	A	
246	N-(2-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
247	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethoxy-benzyl)-oxalamide	A	C	
248	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-methoxy-benzyl)-oxalamide	A		
249	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethyl-benzyl)-oxalamide	A	B	
250	N-{4-[7-(Azetidin-3-ylmethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide	A		
251	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-azetidin-3-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	A	A	
252	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-hydroxy-2-phenyl-ethyl)-oxalamide	B		
253	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(2,4-difluoro-phenyl)-malonamide	A		
254	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(4-fluoro-phenyl)-N'-methyl-malonamide	B		

Table 2

Entry	Name	c-Met	KDR	flt-4
255	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R-phenyl-propyl)-oxalamide	A	B	
256	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R-phenyl-propyl)-oxalamide	A		
257	N-(3,4-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	B	
258	N-(2,6-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
259	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-fluoro-phenyl)-ethyl]-oxalamide	A	A	
260	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenyl-oxalamide	A	B	
261	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-fluoro-phenyl)-oxalamide	A	B	
262	N-(4-Chloro-3-fluoro-phenyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	B	
263	N-(3,4-Dimethoxy-phenyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	B	
264	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-butyl)-oxalamide	A	B	
265	N-(3,3-Dimethyl-butyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	B	
266	N-{5-Chloro-6-[6-methoxy-7-(3-piperidin-1-yl-propoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	A	B	
267	N-{5-Chloro-6-[6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	A	B	
268	N-{5-Chloro-6-[7-(3-diethylamino-propoxy)-6-methoxy-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	A	B	

Table 2

Entry	Name	c-Met	KDR	flt-4
269	N-(4-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A		
270	N-(3,5-Dimethoxy-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A		
271	N-(4-Butyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	B	
272	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-p-tolyl-ethyl)-oxalamide	A	B	
273	N-(3,5-Bis-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A		
274	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-pyrazin-2-ylmethyl-oxalamide	B		
275	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-pyridin-2-ylmethyl-oxalamide	B	B	
276	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	A	A	
277	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	A	A	
278	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-fluoro-3-trifluoromethyl-benzyl)-oxalamide	A	A	
279	N-[2-(2-Bromo-6-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
280	N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N-methyl-oxalamide	B	C	
281	N-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	A	
282	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-fluoro-5-trifluoromethyl-benzyl)-oxalamide	A	A	

Table 2

Entry	Name	c-Met	KDR	flt-4
283	Cyclopropane-1,1-dicarboxylic acid {5-chloro-6-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-pyridin-3-yl}-amide (4-fluoro-phenyl)-amide	A	A	
284	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[1-(4-fluoro-phenyl)-ethyl]-oxalamide	A	A	
285	N-(1S-Benzyl-2-oxo-2-pyrrolidin-1-yl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	C	
286	N-{3-Fluoro-4-[6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	A	A	
287	N-[2-(4-Amino-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	C	
288	2-(4-Benzyl-piperidin-1-yl)-N-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-acetamide	A	A	
289	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenyl]-N'-(4-fluoro-phenyl)-malonamide	A	A	
290	Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide	A	A	
291	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(3-fluoro-phenyl)-malonamide	B	C	
292	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-phenyl-malonamide	A	C	
293	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(4-fluoro-phenyl)-2,2-dimethyl-malonamide	B	B	
294	N-Ethyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	B	
295	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-isopropyl-oxalamide	A	B	
296	N-Butyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	B	
297	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-methoxy-ethyl)-oxalamide	A	B	

Table 2

Entry	Name	c-Met	KDR	flt-4
298	N-Cyclopropylmethyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	A	B	
299	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-morpholin-4-yl-ethyl)-oxalamide	B	A	
300	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-pyrrolidin-1-yl-acetamide	A	B	
301	N-Ethyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N-methyl-oxalamide	A	B	

Table 3

Entry	Compound Name	c-Met	KDR	c-Kit	flt-3	flt-4
1	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	B	A	B
2	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	C	C			
3	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(phenylmethyl)cyclopropane-1,1-dicarboxamide	A	C	B	B	B
4	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-phenylcyclopropane-1,1-dicarboxamide	A	B	B	A	
5	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
6	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A

Table 3

Entry	Compound Name	c-Met	KDR	c-Kit	flt-3	flt-4
7	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	A	A	A	B	A
8	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl)cyclopropane-1,1-dicarboxamide	C	C			
9	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	C	B	C	B
10	N-{4-[(7-chloroquinolin-4-yl)oxy]-3-fluorophenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	C	C	B
11	N-{4-[(7-chloroquinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	B	C	B
12	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
13	N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
14	N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	B	A	A
15	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
16	N-{5-chloro-6-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]pyridin-3-yl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	B	A	A
17	N-[5-chloro-6-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
18	N-[5-chloro-6-({6-(methyloxy)-7-[(phenylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	C	C	B	C
19	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A

Table 3

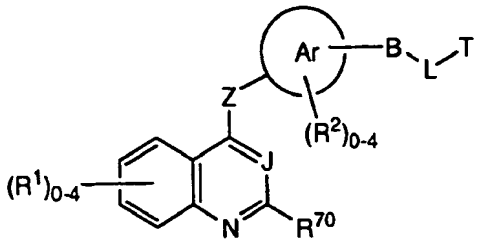
Entry	Compound Name	c-Met	KDR	c-Kit	flt-3	flt-4
20	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	A	A	A	B	A
21	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
22	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	C	A
23	N-(4-fluorophenyl)-N'-[2-methyl-6-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]cyclopropane-1,1-dicarboxamide	A	A	B	B	B
24	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A	A	A	A
25	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloro-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	C			
26	N-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A			
27	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3,5-difluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A			
28	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,5-difluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A			
29	N-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A			
30	N-{3-fluoro-4-[(7-(methyloxy)-6-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A			
31	N-[5-fluoro-2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A			

Table 3

Entry	Compound Name	c-Met	KDR	c-Kit	flt-3	flt-4
32	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,3,5-trifluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A			
33	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	B			
34	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	B			
35	N-(3-fluoro-4-{[6-hydroxy-7-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	A	A			
36	N-(4-fluorophenyl)-N'-[2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide	A	A			

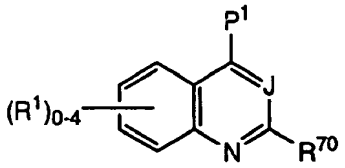
What is claimed is:

1. A process for preparing a compound of Formula **I**,

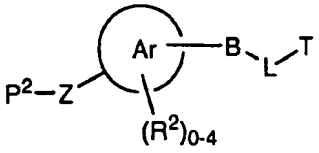


I

comprising reaction of a compound of Formula **II**, with a compound of Formula **III**



II



III

wherein,

each R^1 is independently selected from halogen, $-OR^3$, $-NO_2$, $-NH_2$, $-NR^3R^3$, $-D-R^{50}$ and optionally substituted C_{1-6}alkyl;

R^{70} is selected from -H, halogen, $-OR^3$, $-S(O)_{0-2}R^3$, $-NO_2$, $-NH_2$, $-NR^3R^3$, and optionally substituted C_{1-6}alkyl;

J is selected from =N-, =C(H)-, =C(halogen)-, and =C(CN)-;

Z is selected from $-S(O)_{0-2}$-, -O-, and $-NR^5$-;

R^5 is selected from -H, optionally substituted C_{1-6}alkyl, and optionally substituted aryl C_{1-6}alkyl;

Ar is either a five- or six-membered arylene or a five- or six-membered heteroarylene containing between one and three heteroatoms;

R^2 is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted C_{1-6}alkyl;

B is selected from absent, $-N(R^{13})$-, $-N(SO_2R^{13})$-, -O-, $-S(O)_{0-2}$-, and -C(=O)-;

L is selected from absent, -C(=S)N(R^{13})-, -C(=NR^{14})N(R^{13})-, -SO_2N(R^{13})-, -SO_2-, -C(=O)N(R^{13})-, -N(R^{13})-, -C(=O)C_{1-2}alkylN(R^{13})-, -N(R^{13})C_{1-2}alkylC(=O)-, -C(=O)C_{0-1}alkylC(=O)N(R^{13})-, -C(=O)-, -C_{0-4}alkylene-, -C(=O)C_{0-1}alkylC(=O)OR^3-, -C(=NR^{14})C_{0-1}alkylC(=O)-, -C(=O)C_{0-1}alkylC(=O)-, and an optionally substituted four- to six-membered heterocyclyl containing between one and three annular heteroatoms and comprising at least one nitrogen;

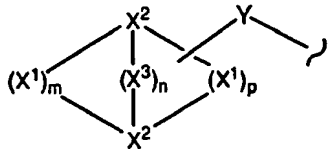
T is selected from -H, -R^{13}, -C_{0-4}alkyl, -C_{0-4}alkylQ, -OC_{0-4}alkylQ, -C_{0-4}alkylOQ, -N(R^{13})C_{0-4}alkylQ, -SO_2C_{0-4}alkylQ, -C(=O)C_{0-4}alkylQ, -C_{0-4}alkylN(R^{13})Q, and -C(=O)N(R^{13})C_{0-4}alkylQ, wherein each of the aforementioned C_{0-4}alkyl is optionally substituted;

Q is a five- to ten-membered ring system, optionally substituted with between zero and four of R^{20};

R^{20} is selected from -H, halogen, trihalomethyl, -CN, -NO_2, -NH_2, -OR^3, -NR^3R^3, -S(O)$_{0-2}R^3$, -$SO_2NR^3R^3$, -CO_2R^3, -C(O)NR^3R^3, -N(R^3)SO_2R^3, -N(R^3)C(O)R^3, -N(R^3)CO_2R^3, -C(O)R^3, and optionally substituted C_{1-6}alkyl;

D is selected from -O-, -S(O)$_{0-2}$-, and -NR^{15}-;

R^{50} is either R^3, or according to formula **IV**;



IV

wherein X^1, X^2, and optionally X^3, represent the atoms of a saturated bridged ring system, said saturated bridged ring system comprising up to four annular heteroatoms represented by any of X^1, X^2, and X^3; wherein,

each X^1 is independently selected from -C(R^6)R^7-, -O-, -S(O)$_{0-2}$-, and -NR^8-;

each X^2 is independently an optionally substituted bridgehead methine or a bridgehead nitrogen;

each X^3 is independently selected from -C(R^6)R^7-, -O-, -S(O)$_{0-2}$-, and -NR^8-;

Y is either:

an optionally substituted C_{1-6}alkylene linker, between D and either 1) any annular atom of the saturated bridged ring system, except X^2 when X^2 is a bridgehead nitrogen, or 2) any heteroatom, represented by any of R^6 or R^7; provided there are at least two carbon atoms between D and any annular heteroatom of the saturated bridged ring system or any heteroatom represented by any of R^6 or R^7;

or Y is absent, when Y is absent, said saturated bridged ring system, is directly attached to D via an annular carbon of said saturated bridged ring system, unless D is $-SO_2-$, in which case said saturated bridged ring system, is directly attached to D via an any annular atom of said saturated bridged ring system;

m and p are each independently one to four;

n is zero to two, when n is zero, then there is a single bond between the two bridgehead X^2's;

R^6 and R^7 are each independently selected from -H, halogen, trihalomethyl, -CN, $-NH_2$, $-NO_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-NCO_2R^3$, $-C(O)R^3$, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, optionally substituted heterocyclyl, optionally substituted heterocyclyl a C_{1-6}lkyl, and a bond to either Y or D; or

R^6 and R^7, when taken together are oxo; or

R^6 and R^7, when taken together with a common carbon to which they are attached, form a optionally substituted three- to seven-membered spirocyclyl, said optionally substituted three- to seven-membered spirocyclyl optionally containing at least one additional annular heteroatom selected from N, O, S, and P;

R^8 is selected from $-R^3$, Y, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-SO_2R^3$, and $-C(O)R^3$;

R^{13} is selected from -H, $-C(=O)R^3$, $-C(=O)OR^3$, $-C(=O)SR^3$, $-SO_2R^3$, $-C(=O)N(R^3)R^3$, and optionally substituted C_{1-6}alkyl;

two R^{13}, together with the atom or atoms to which they are attached, can combine to form a heteroalicyclic optionally substituted with between one and four of R^{60}, said heteroalicyclic comprising up to four annular heteroatoms, and said heteroalicyclic optionally comprising an aryl or heteroaryl fused thereto, in which case said aryl or heteroaryl is optionally substituted with an additional one to four of R^{60};

R^{14} is selected from -H, $-NO_2$, $-NH_2$, $-N(R^3)R^3$, -CN, $-OR^3$, optionally substituted C_{1-6}alkyl, optionally substituted heteroalicyclyl C_{1-6}alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl and optionally substituted heteroalicyclic;

R^{15} is a group $-M^1-M^2$, wherein M^1 is selected from absent, $-C(=S)N(R^{13})-$, $-C(=NR^{14})N(R^{13})-$, $-SO_2N(R^{13})-$, $-SO_2-$, $-C(=O)N(R^{13})-$, $-C(=O)C(=O)N(R^{13})-$, $-C_{0-4}$alkylene-, -C(=O)-, and an optionally substituted four to six-membered heterocyclyl containing between one and three heteroatoms but comprising at least one nitrogen; and M^2 is selected from -H, $-C_{0-6}$alkyl, alkoxy, $-C(=O)C_{0-4}$alkylQ, $-C_{0-4}$alkylQ, $-OC_{0-4}$alkylQ-, $-N(R^{13})C_{0-4}$alkylQ-, and $-C(=O)N(R^{13})C_{0-4}$alkylQ;

R^{60} is selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted heteroaryl C_{1-6}alkyl, and optionally substituted aryl C_{1-6}alkyl;

two of R^{60}, when attached to a non-aromatic carbon, can be oxo;

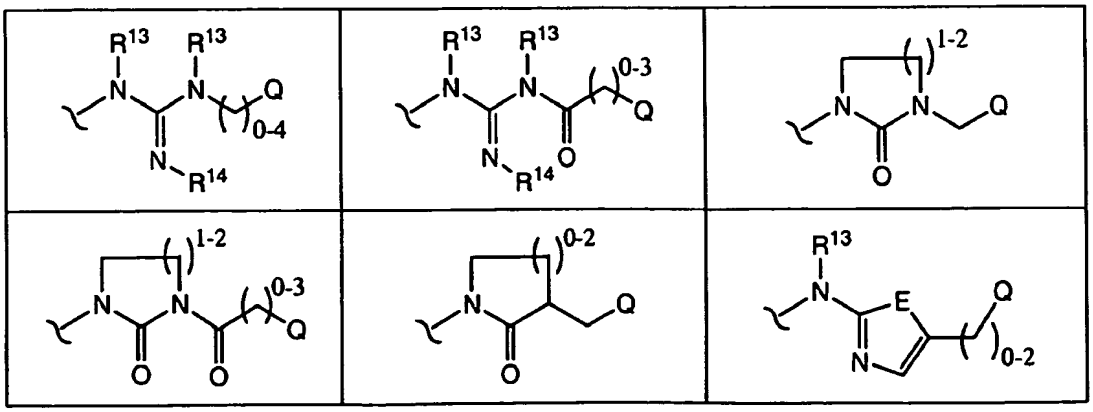
P^1 is a suitable leaving group; and

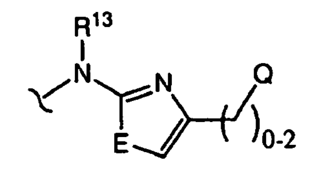
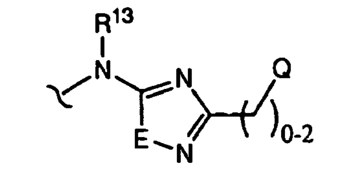
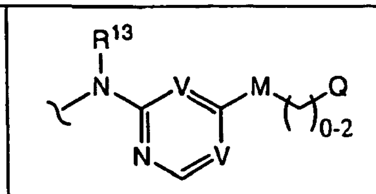
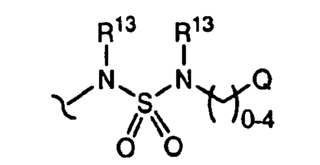
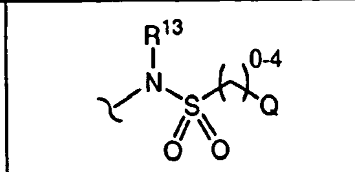
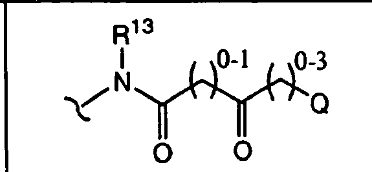
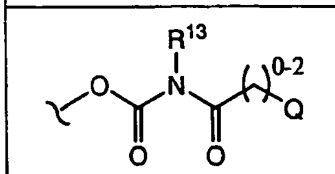
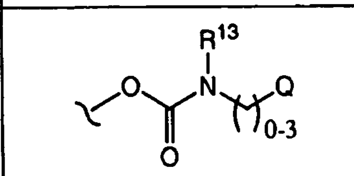
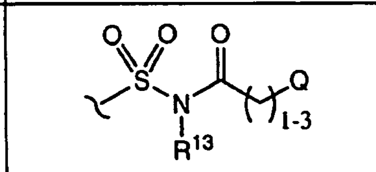
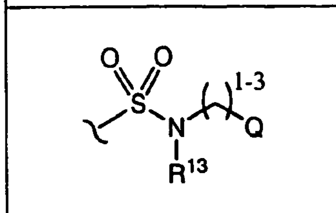
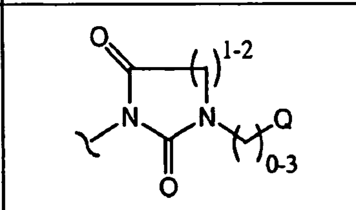
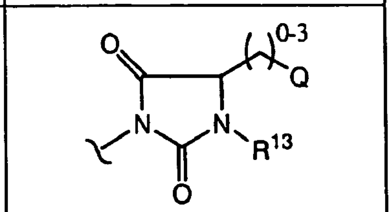
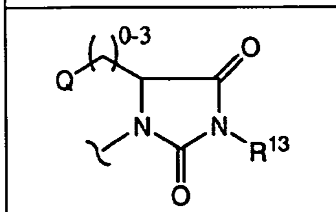
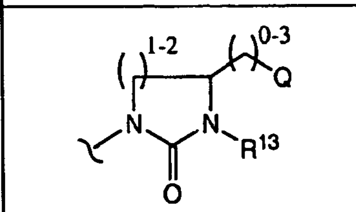
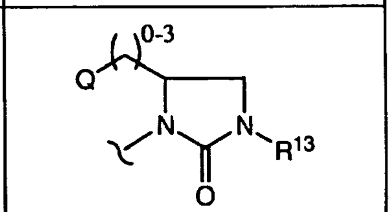
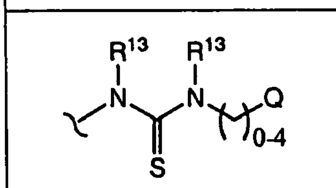
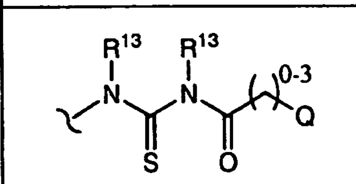
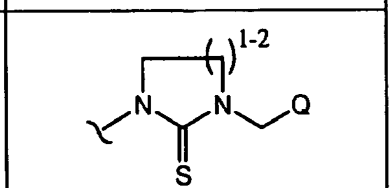
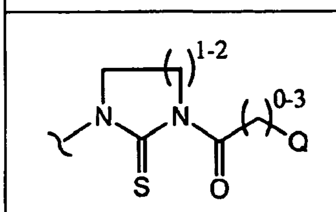
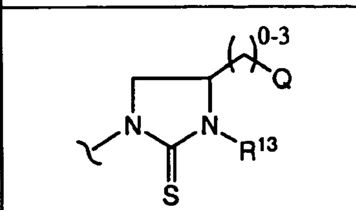
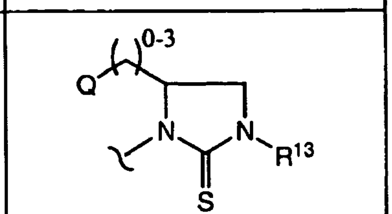
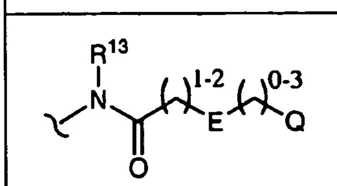
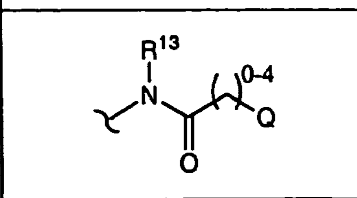
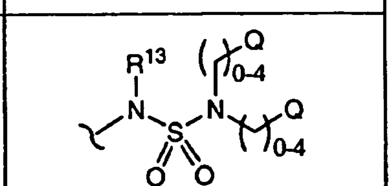
P^2 is selected from -H, a metal, and a group removed *in-situ* when combining **II** and **III** to make **I**.

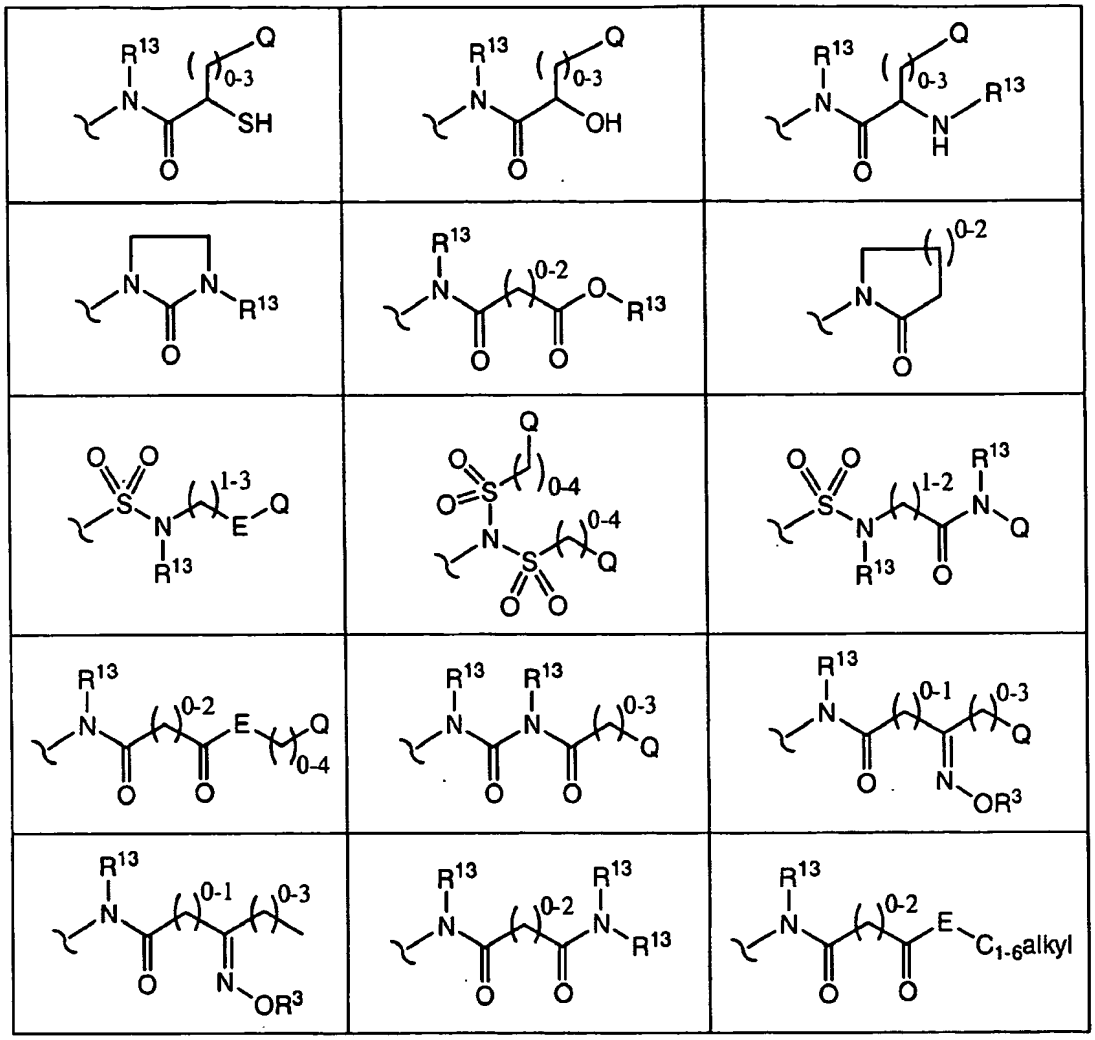
2. The process according to claim 1, wherein Ar is *para*-phenylene as defined by the substitution pattern of -Z- and -B-L-T.

3. The process according to claim 2, wherein Z is either -O- or $-NR^5-$.

4. The process according to claim 3, wherein -B-L-T is selected from the following:





wherein Q, R^{20}, and R^{13} are as defined above; each E is selected from -O-, -N(R^{13})-, -CH_2-, and -S(O)$_{0-2}$-; M is selected from -O-, -N(R^{13})-, -CH_2-, and -C(=O)N(R^{13})-; each V is independently either =N- or =C(H)-; each methylene in any of the above formulae is independently optionally substituted with R^{25}; and R^{25} is selected from halogen, trihalomethyl, -CN, -NO_2, -NH_2, -OR^3, -NR^3R^3, -S(O)$_{0-2}R^3$, -$SO_2NR^3R^3$, -CO_2R^3, -C(O)NR^3R^3, -N(R^3)SO_2R^3, -N(R^3)C(O)R^3, -N(R^3)CO_2R^3, -C(O)R^3, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, heteroaryl C_{1-6}alkyl, and optionally substituted C_{1-6}alkyl; two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form an optionally substituted three- to seven-membered alicyclic or heteroalicyclic; two of R^{25} on a single carbon can be oxo.

5. The process according to claim 4, wherein there are only two of R^1, one of R^1 is -D-R^{50} and the other R^1 is -OR^{3a}.

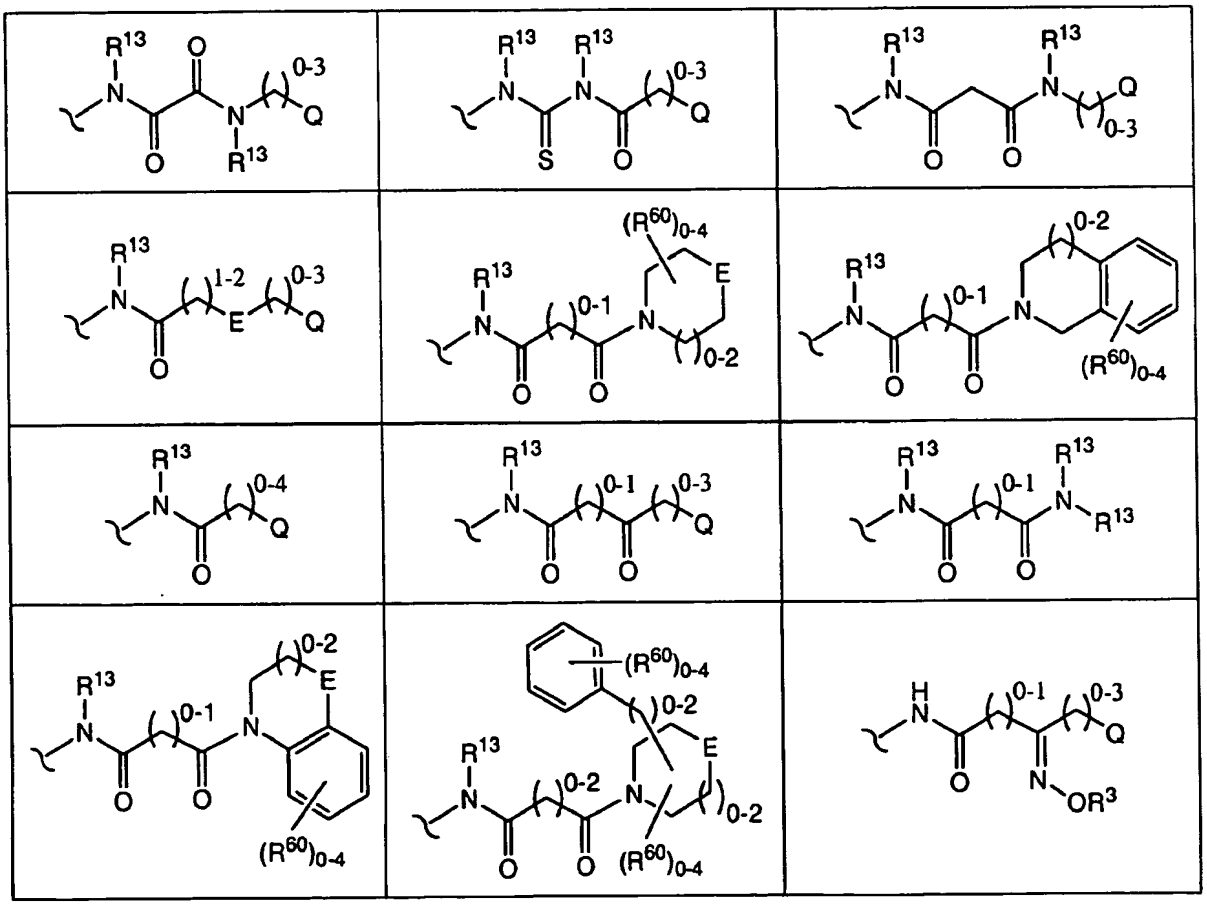
6. The process according to claim 5, wherein D is -O-.

7. The process according to claim 6, wherein -O-R^{50} and -OR^{3a} are interchangeably located at the 6-position and 7-position of the quinazoline or quinoline according to Formula I.

8. The process according to claim 7, wherein -OR^{3a} is -OH or optionally substituted -OC_{1-6}alkyl.

9. The process according to claim 8, wherein J is =N- or =C(H)-.

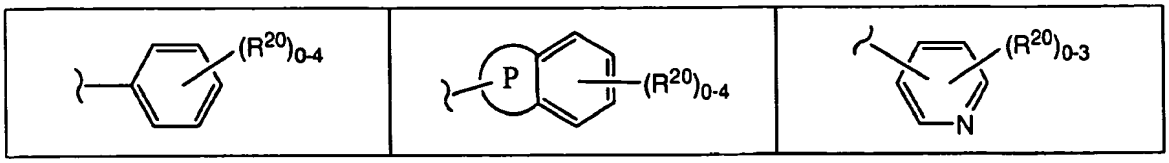
10. The process according to claim 9, wherein -B-L-T is selected from:



wherein Q, R^{20}, R^{13}, E, and R^{60} are as defined above; each methylene in any of the above formulae, other than those in a depicted ring, is independently optionally substituted with R^{25}; and R^{25} is selected from halogen, trihalomethyl, oxo, -CN, -NO_2, -NH_2, -OR^3, -NR^3R^3, -$S(O)_{0-2}R^3$, -$SO_2NR^3R^3$, -CO_2R^3, -$C(O)NR^3R^3$, -$N(R^3)SO_2R^3$, -$N(R^3)C(O)R^3$, -$N(R^3)CO_2R^3$, -$C(O)R^3$, optionally substituted aryl, optionally substituted aryl C_{1-6}alkyl, heteroaryl C_{1-6}alkyl,

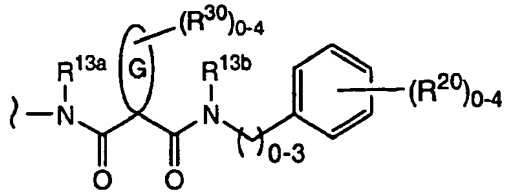
and optionally substituted C_{1-6}alkyl; two of R^{25}, together with the carbon or carbons to which they are attached, can combine to form a three- to seven-membered optionally substituted alicyclic or heteroalicyclic.

11. The process according to claim 10, wherein Q is selected from the following three formula:

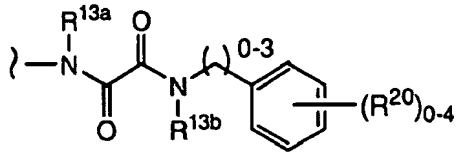


wherein R^{20} is defined as above, and P is a five- to seven-membered ring, including the two shared carbons of the aromatic ring to which P is fused, P optionally containing between one and three heteroatoms.

12. The process according to claim 11, wherein -B-L-T is either of formula V or formula VI,



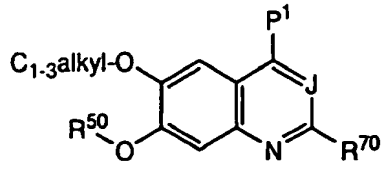
V



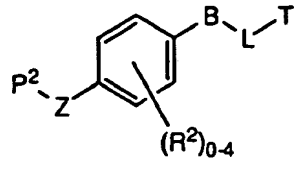
VI

wherein R^{20} is defined as above; G is either an optionally substituted cycloalkyl or an optionally substituted heteroalicyclic; each R^{30} is independently selected from halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^3$, $-NR^3R^3$, $-S(O)_{0-2}R^3$, $-SO_2NR^3R^3$, $-CO_2R^3$, $-C(O)NR^3R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)CO_2R^3$, $-C(O)R^3$, and optionally substituted C_{1-6}alkyl; and R^{3a} and R^{3b} are each independently selected from -H and optionally substituted C_{1-6}alkyl.

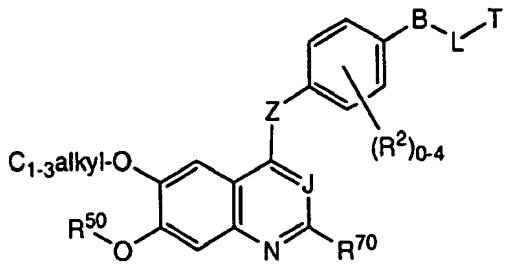
13. The process according to claim 12, wherein a compound of formula **IIa** is combined with a compound of formula **IIIa** to make a compound of formula **Ia**,



IIa



IIIa



Ia

wherein -B-L-T, Z, J, R^{50}, and R^2 are as defined above; R^{70} is selected from -H, $-NO_2$, $-NH_2$, and $-NR^3R^3$; provided when Z is $-N(R^5)-$ that R^5 is selected from -H, C_{1-3}alkyl, and aryl C_{1-3}alkyl; P^1 is selected from halogen, optionally substituted alkyl-$S(O)_{0-2}$-, optionally substituted arylsulfonate, optionally substituted alkylsulfonate, a group containing boron, an azide, a group containing phosphorus, and a metal; and P^2 is selected from -H and a metal.

14. The process according to claim 13, wherein P^2 is selected from -H, lithium, sodium, potassium, cesium, copper, palladium, and titanium.

15. The process according to claim 14, wherein Z is -O-.

16. The process according to claim 15, wherein P^1 is selected from chlorine, bromine, a toluene sulfonate, and trifluoromethansulfonate.

17. The process according to claim 16, wherein R^{70} is -H.

18. The process according to claim 17, wherein J is =C(H)-.

19. The process according to claim 18, wherein R^2 is fluorine and there are up to three of R^2.

20. The process according to claim 19, wherein **IIa** and **IIIa** are heated together, optionally with a base, optionally with microwave radiation, to form **Ia**.

21. The process according to claim 20, wherein the base is selected from an organic base, an inorganic base, and a combination of an organic base and an inorganic base.

22. The process according to claim 21, wherein the base is selected from 2,6-lutidine, 4-N,N-dimethylaminopyridine, and a metal carbonate.

23. The process according to claim 22, wherein **IIa** and **IIIa** are heated together in a solvent with said base, at between about 40°C and 200°C for between about one hour and twenty-four hours to form **Ia**.

24. The process according to claim 23, wherein the solvent is an organic solvent.

25. The process according to claim 24, wherein one molar equivalent of **IIa** is combined with between about one quarter and four molar equivalents of **IIIa**.

26. The process according to claim 25, wherein one molar equivalent of **IIa** is combined with more than one but less than two molar equivalents of **IIIa**.

27. The process according to claim 26, wherein **IIa** is combined with **IIIa** and said base in an aromatic solvent to form a mixture, and said mixture is heated to between about 100°C and 200°C for between about one and ten hours to form **Ia**.

28. The process according to claim 27, wherein the aromatic solvent is an optionally substituted benzene.

29. The process according to claim 28, wherein the aromatic solvent is bromobenzene.

30. The process according to claim 29, wherein the base is 4-N,N-dimethylaminopyridine.

31. The process according to claim 30, wherein said mixture is heated to reflux for between about three and seven hours.

32. The process according to claim 31, wherein said mixture is heated to reflux for between about four and six hours.

33. The process according to claim 26, wherein **IIa** is combined with **IIIa** and said base in a non-aromatic solvent to form a mixture, and said mixture is heated to between about 40°C and 100°C for between about one and twenty hours to form **Ia**.

34. The process according to claim 33, wherein the non-aromatic solvent comprises a functional group selected from an amide, and ether, a nitrile, a halide, an ester, an amine, and a ketone.

35. The process according to claim 34, wherein the non-aromatic solvent is N,N-dimethylacetamide.

36. The process according to claim 35, wherein the base is potassium carbonate.

37. The process according to claim 36, wherein said mixture is heated to about 50°C between about ten and twenty hours.

38. The process according to claim 37, wherein the aromatic solvent is an optionally substituted pyridine.

39. The process according to claim 38, wherein the aromatic solvent is 2,6-lutidine.

40. The process according to claim 39, wherein the base is 2,6-lutidine.

41. The process according to claim 40, wherein said mixture is heated to reflux for between about three and seven hours.

42. The process according to claim 41, wherein said mixture is heated to reflux for between about four and six hours.

43. The process according to claim 25, wherein one molar equivalent of **IIIa** is combined with more than one but less than two molar equivalents of **IIa**.

44. The process according to claim 43, wherein **IIa** is combined with **IIIa** and said base in an aromatic solvent to form a mixture, and said mixture is heated to between about 100°C and 200°C for between about ten and twenty hours to form **Ia**.

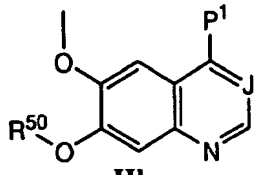
45. The process according to claim 44, wherein the aromatic solvent is an optionally substituted pyridine.

46. The process according to claim 45, wherein the aromatic solvent is 2,6-lutidine.

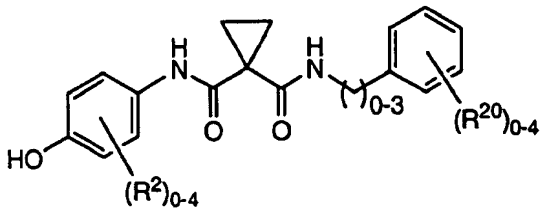
47. The process according to claim 46, wherein the base is 2,6-lutidine.

48. The process according to claim 47, wherein said mixture is heated to between about 150°C and 200°C for between about fifteen and twenty hours.

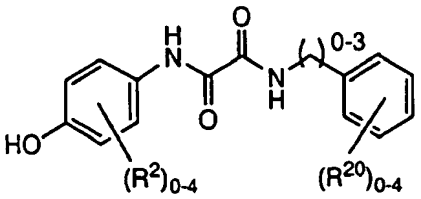
49. The process according to any of claims 20 - 48, wherein a compound of formula **IIb** is substituted for the compound of formula **IIa**, and either a compound of formula **IIIb** or a compound of formula **IIIc** is substituted for the compound of formula **IIIa**, in order to make a compound of formula **Ib** or a compound of formula **Ic**, respectively,



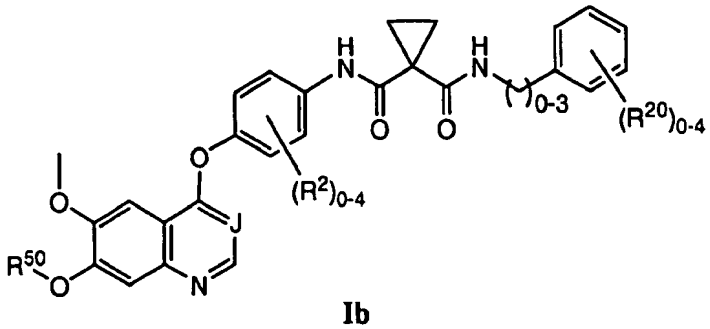
IIb



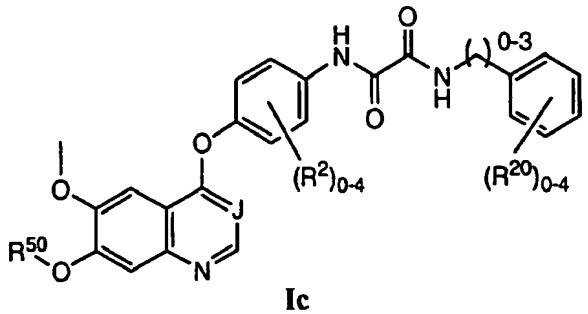
IIIb



IIIc



Ib



Ic

wherein J, R^{50}, R^{20} and R^2 are as defined above.

50. The process according to claim 49, wherein R^2, if present, is fluorine.

51. The process according to claim 50, wherein R^2, if present, is up to two fluorines *ortho* to the oxygen of the phenylene.

52. The process according to claim 1, used to make a compound listed in Table 4.

Table 4

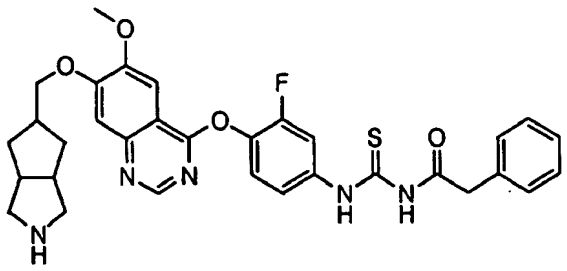
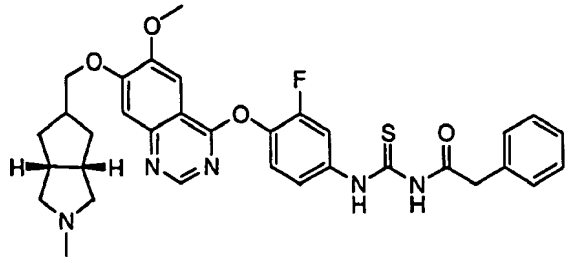
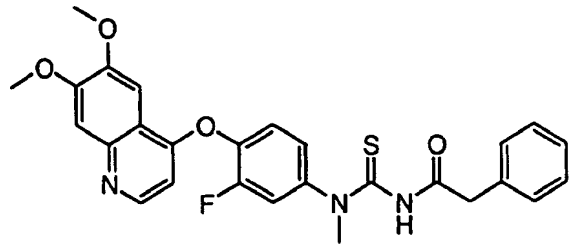
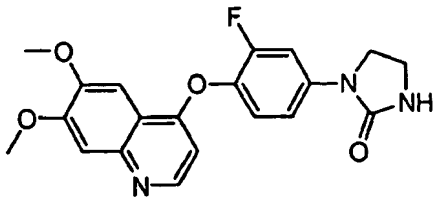
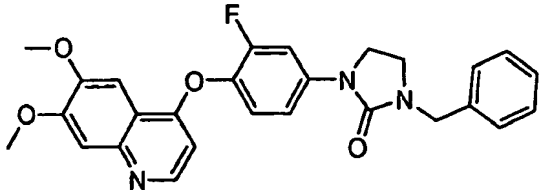
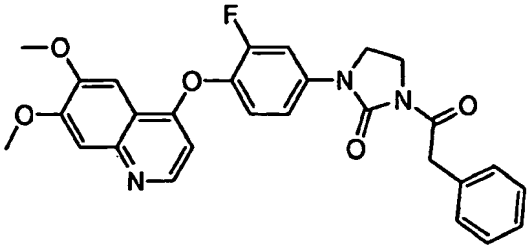
Entry	Name	Structure
1	N-[({3-fluoro-4-[(6-(methyloxy)-7-{[(3aR,6aS)-octahydrocyclopenta[c]pyrrol-5-ylmethyl]oxy}quinazolin-4-yl)oxy]phenyl}amino)carbonothioyl]-2-phenylacetamide	
2	N-{[(3-fluoro-4-{[7-({[(3aR,6aS)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-yl]oxy}phenyl)amino]carbonothioyl}-2-phenylacetamide	
3	N-{[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)(methyl)amino]carbonothioyl}-2-phenylacetamide	
4	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)imidazolidin-2-one	
5	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylmethyl)imidazolidin-2-one	
6	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylacetyl)imidazolidin-2-one	

Table 4

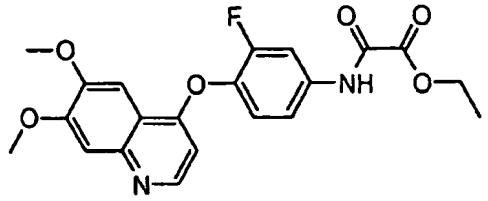
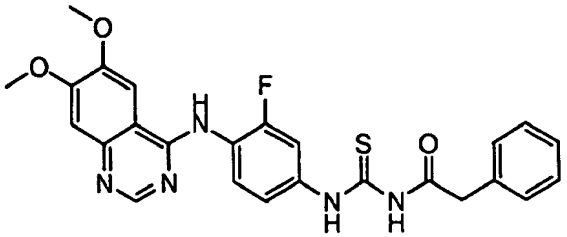
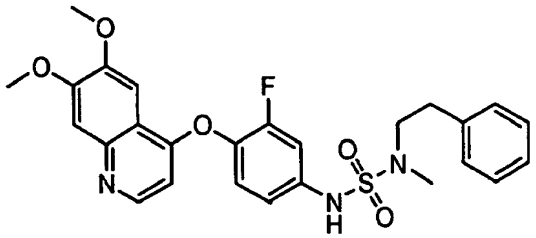
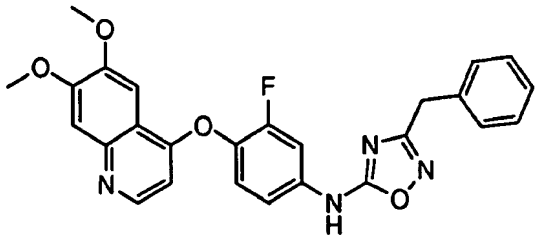
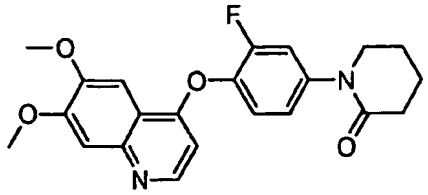
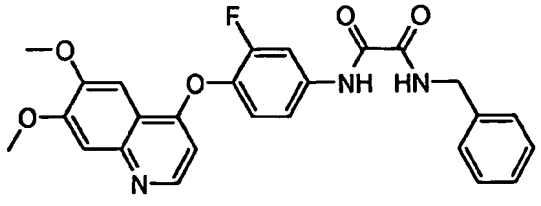
Entry	Name	Structure
7	ethyl [(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino](oxo)acetate	
8	N-{[(4-{[6,7-bis(methyloxy)quinazolin-4-yl]amino}-3-fluorophenyl)amino]carbonothioyl}-2-phenylacetamide	
9	N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-methyl-N-(2-phenylethyl)sulfamide	
10	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylmethyl)-1,2,4-oxadiazol-5-amine	
11	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)piperidin-2-one	
12	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(phenylmethyl)ethanediamide	

Table 4

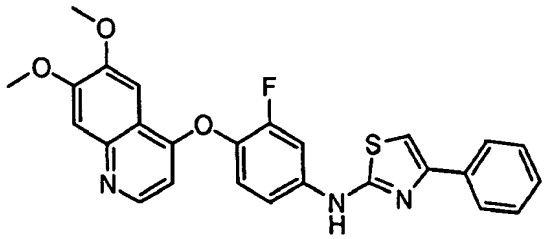
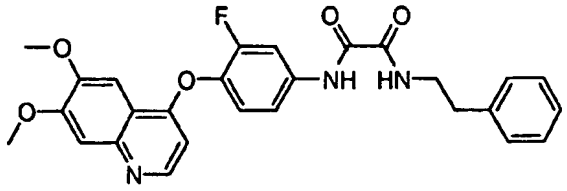
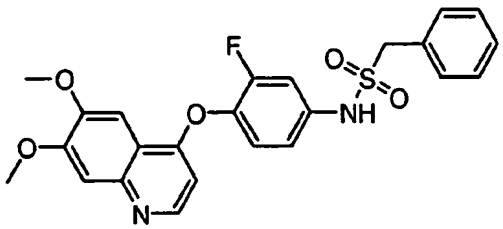
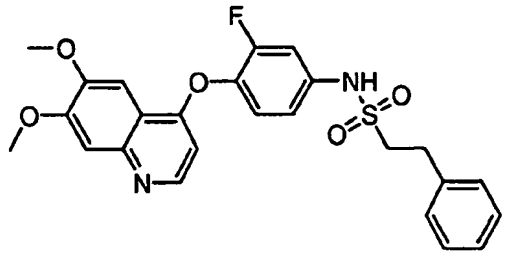
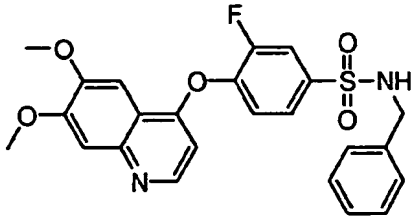
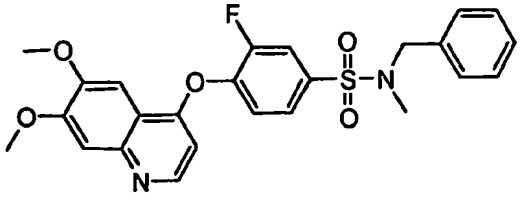
Entry	Name	Structure
13	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-4-phenyl-1,3-thiazol-2-amine	
14	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylethyl)ethanediamide	
15	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-1-phenylmethanesulfonamide	
16	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-2-phenylethanesulfonamide	
17	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(phenylmethyl)benzenesulfonamide	
18	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(phenylmethyl)benzenesulfonamide	

Table 4

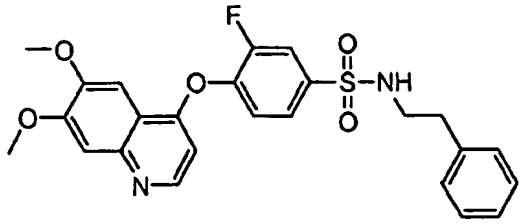
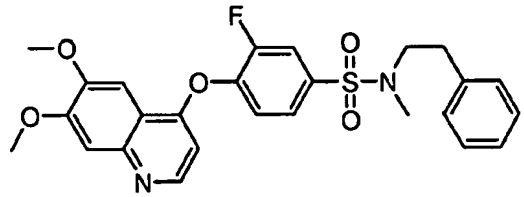
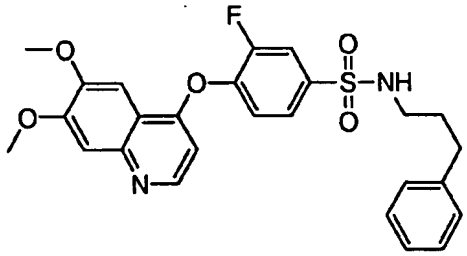
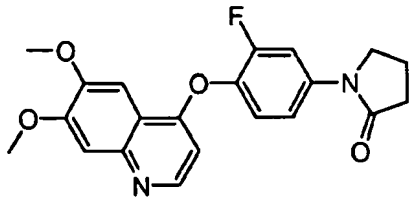
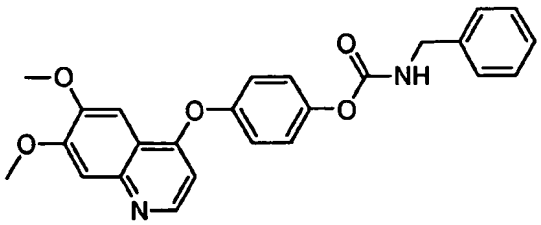
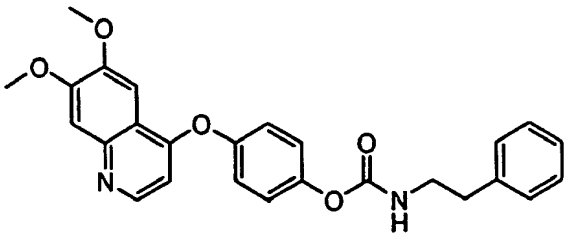
Entry	Name	Structure
19	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(2-phenylethyl)benzenesulfonamide	
20	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(2-phenylethyl)benzenesulfonamide	
21	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-(3-phenylpropyl)benzenesulfonamide	
22	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)pyrrolidin-2-one	
23	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (phenylmethyl)carbamate	
24	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (2-phenylethyl)carbamate	

Table 4

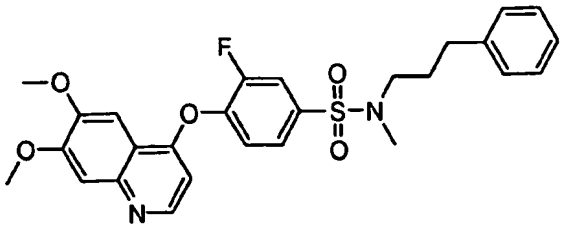
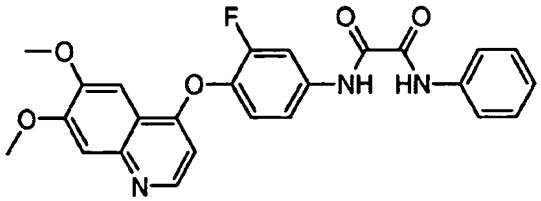
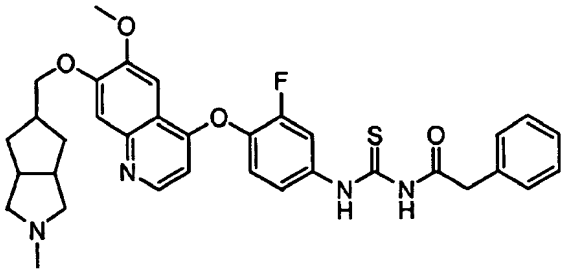
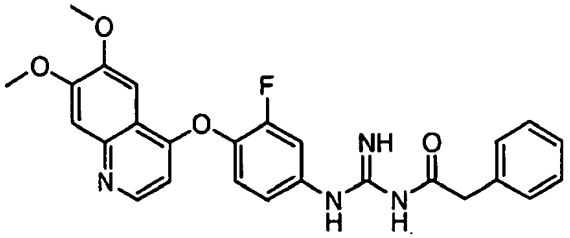
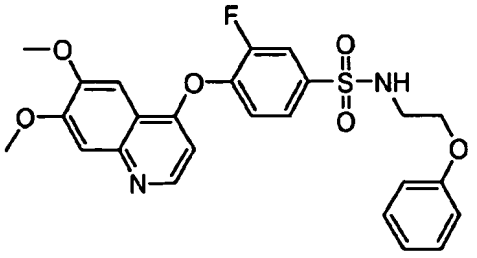
Entry	Name	Structure
25	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-methyl-N-(3-phenylpropyl)benzenesulfonamide	
26	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-phenylethanediamide	
27	N-{[(3-fluoro-4-{[7-{[(2-methyloctahydrocyclopenta[c]pyrrol-5-yl)methyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}phenyl)amino]carbonothioyl}-2-phenylacetamide	
28	N-[(Z)-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino](imino)methyl]-2-phenylacetamide	
29	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-N-[2-(phenyloxy)ethyl]benzenesulfonamide	

Table 4

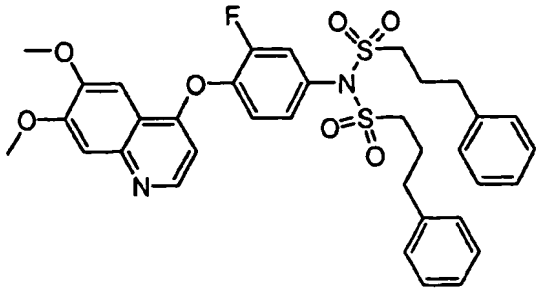
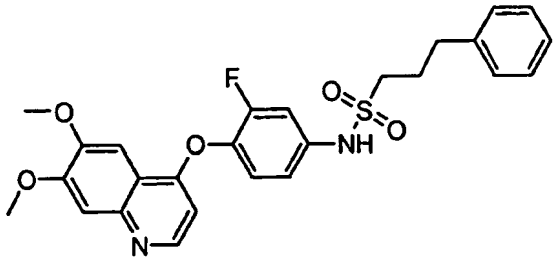
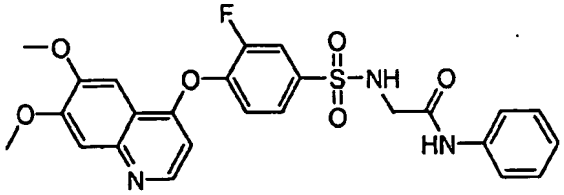
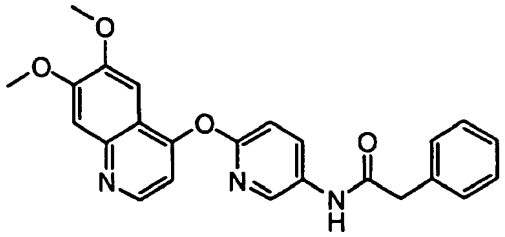
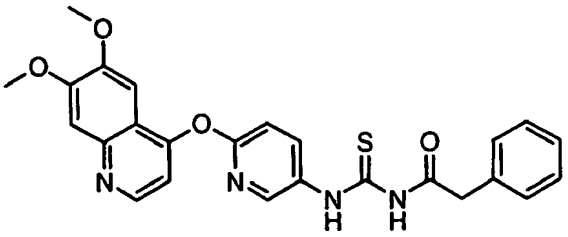
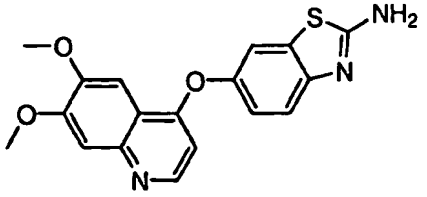
Entry	Name	Structure
30	N,N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-bis-(3-phenylpropane-1-sulfonamide)	
31	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-phenylpropane-1-sulfonamide	
32	N2-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)sulfonyl]-N1-phenylglycinamide	
33	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-2-phenylacetamide	
34	N-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide	
35	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-amine	

Table 4

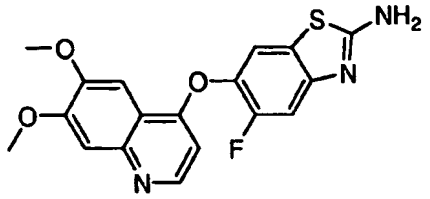
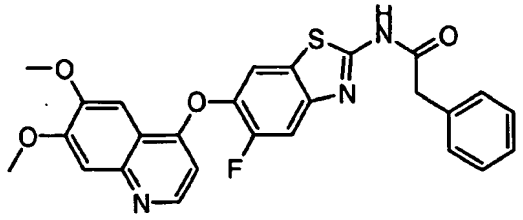
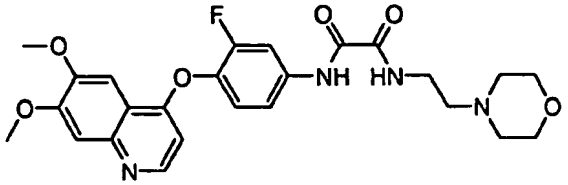
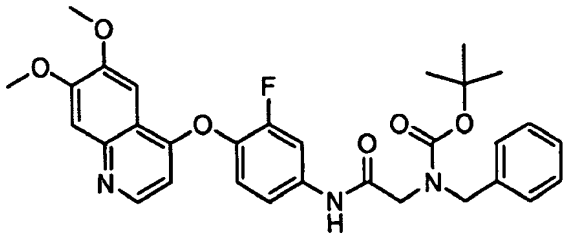
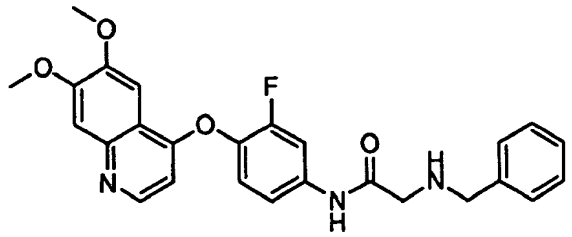
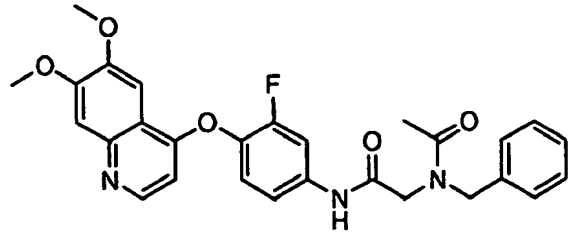
Entry	Name	Structure
36	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-amine	
37	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-phenylacetamide	
38	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-morpholin-4-ylethyl)ethanediamide	
39	benzyl-{[4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylcarbamoyl]-methyl}-carbamic acid tert-butyl ester	
40	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(phenylmethyl)glycinamide	
41	N2-acetyl-N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(phenylmethyl)glycinamide	

Table 4

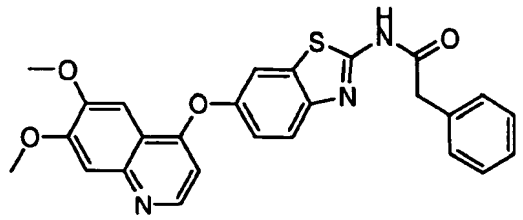
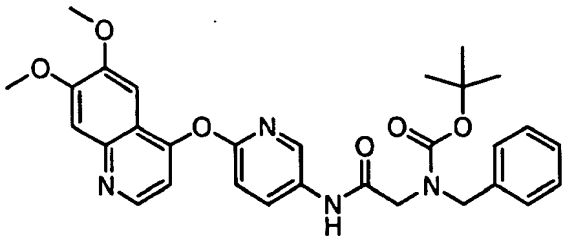
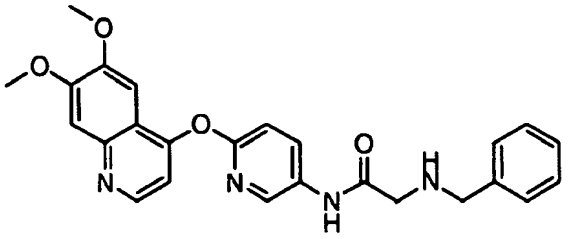
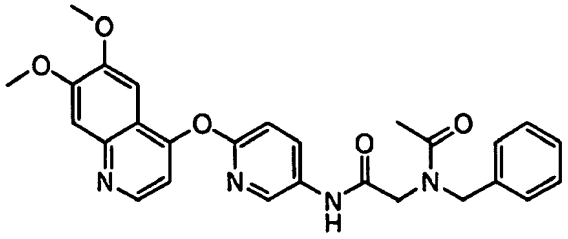
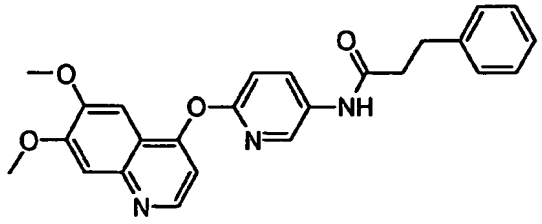
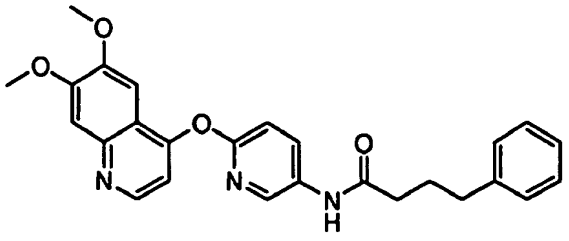
Entry	Name	Structure
42	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-yl)-2-phenylacetamide	
43	benzyl-{[6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-ylcarbamoyl]-methyl}-carbamic acid tert-butyl ester	
44	N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-(phenylmethyl)glycinamide	
45	N2-acetyl-N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-(phenylmethyl)glycinamide	
46	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-3-phenylpropanamide	
47	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-4-phenylbutanamide	

Table 4

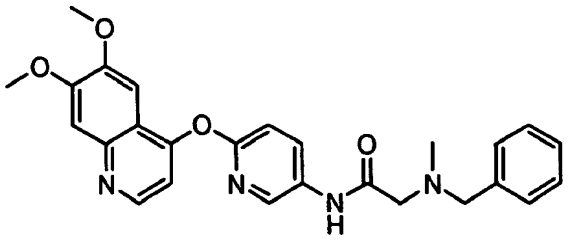
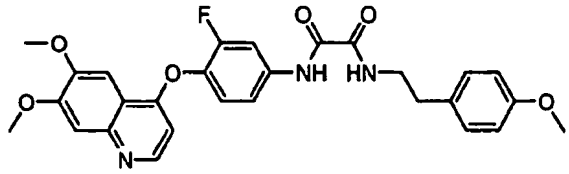
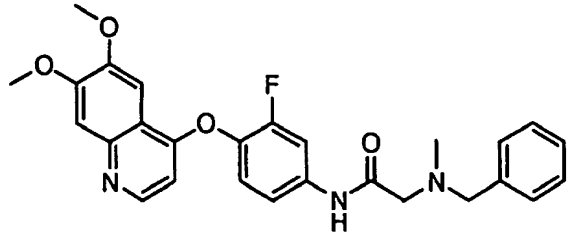
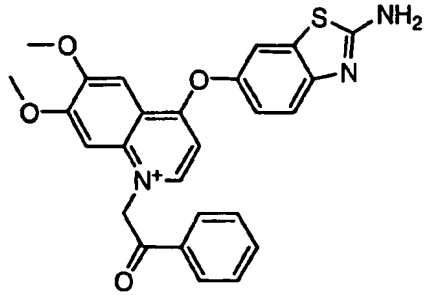
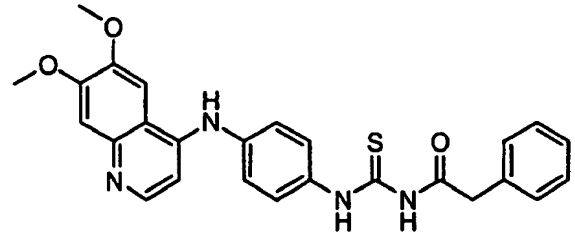
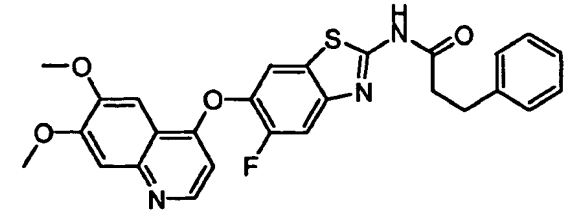
Entry	Name	Structure
48	N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N2-methyl-N2-(phenylmethyl)glycinamide	
49	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{2-[4-(methyloxy)phenyl]ethyl}ethanediamide	
50	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-(phenylmethyl)glycinamide	
51	4-[(2-amino-1,3-benzothiazol-6-yl)oxy]-6,7-bis(methyloxy)-1-(2-oxo-2-phenylethyl)quinolinium	
52	N-{[(4-{[6,7-bis(methyloxy)quinolin-4-yl]amino}phenyl)amino]carbonothioyl}-2-phenylacetamide	
53	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-3-phenylpropanamide	

Table 4

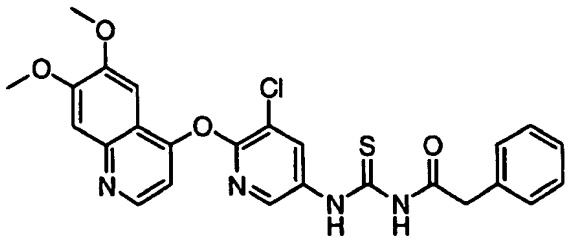
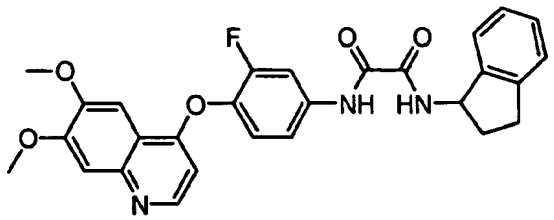
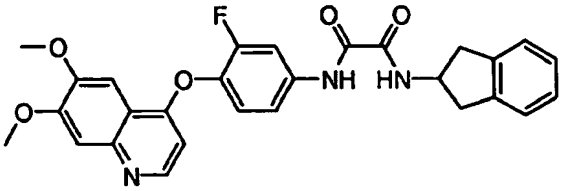
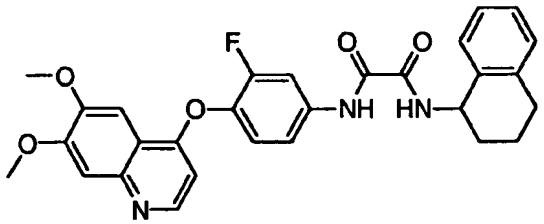
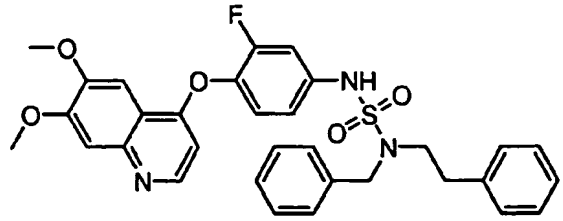
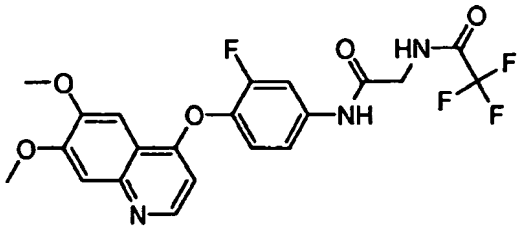
Entry	Name	Structure
54	N-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide	
55	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2,3-dihydro-1H-inden-1-yl)ethanediamide	
56	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2,3-dihydro-1H-inden-2-yl)ethanediamide	
57	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydronaphthalen-1-yl)ethanediamide	
58	N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-(2-phenylethyl)-N-(phenylmethyl)sulfamide	
59	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(trifluoroacetyl)glycinamide	

Table 4

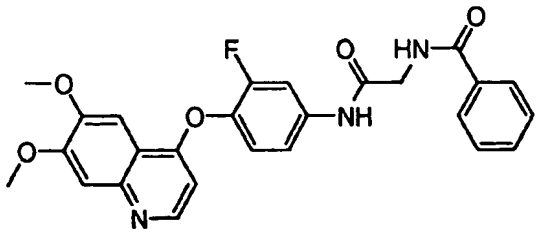
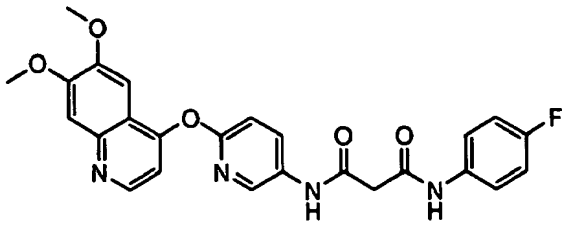
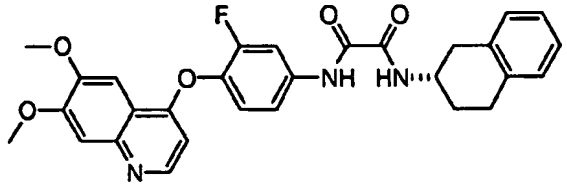
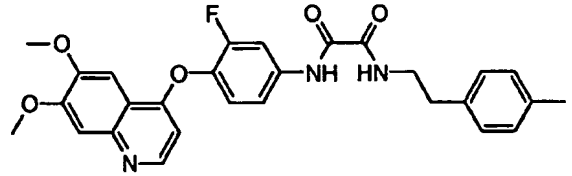
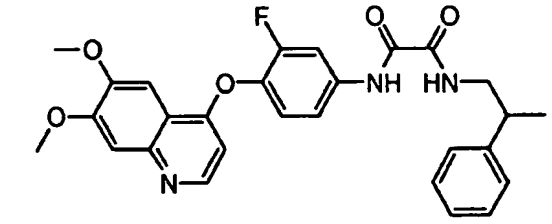
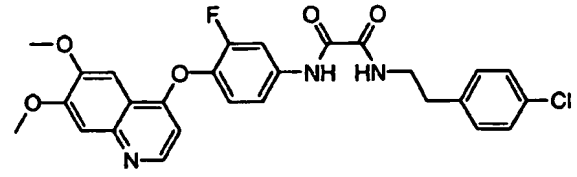
Entry	Name	Structure
60	N-{[4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylcarbamoyl]-methyl}-benzamide	
61	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-N'-(4-fluorophenyl)propanediamide	
62	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2S)-1,2,3,4-tetrahydronaphthalen-2-yl]ethanediamide	
63	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(4-methylphenyl)ethyl]ethanediamide	
64	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(2-phenylpropyl)ethanediamide	
65	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(4-chlorophenyl)ethyl]ethanediamide	

Table 4

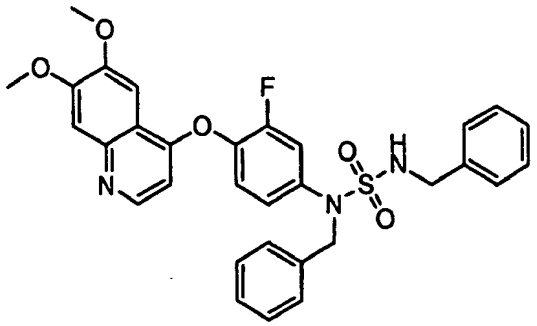
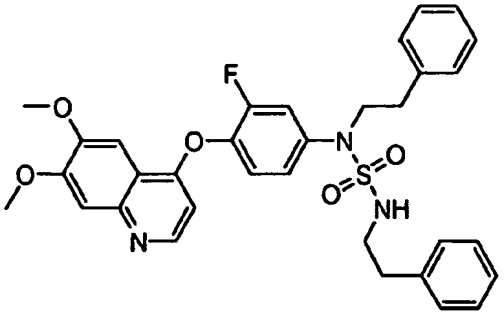
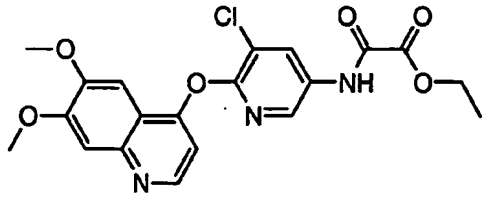
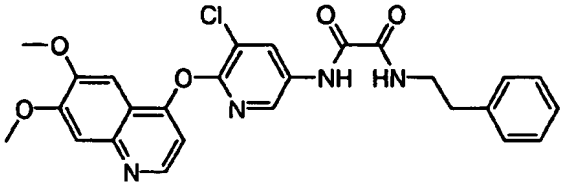
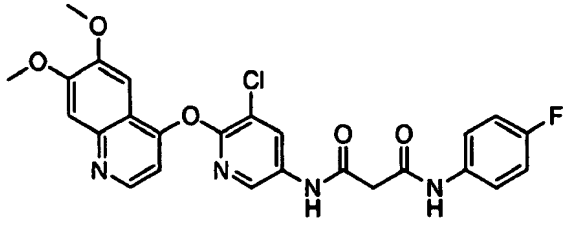
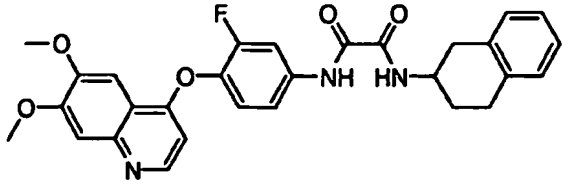
Entry	Name	Structure
66	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N,N'-bis(phenylmethyl)sulfamide	
67	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N,N'-bis(2-phenylethyl)sulfamide	
68	ethyl [(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino](oxo)acetate	
69	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl)ethanediamide	
70	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)propanediamide	
71	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydronaphthalen-2-yl)ethanediamide	

Table 4

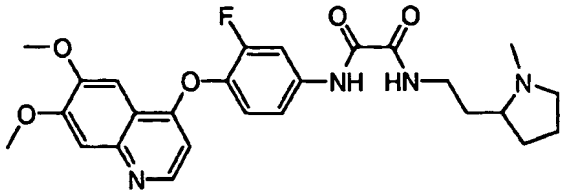
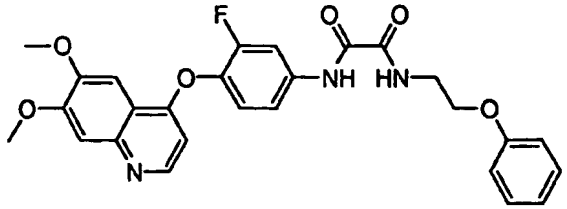
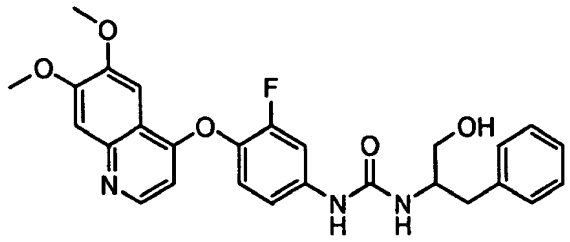
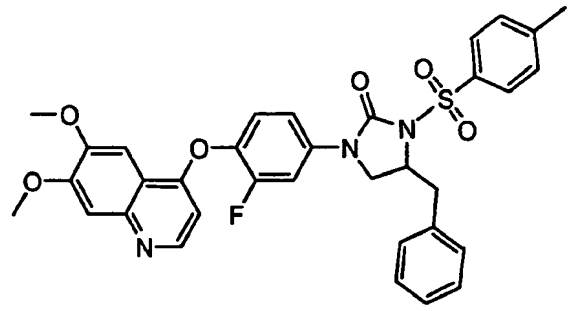
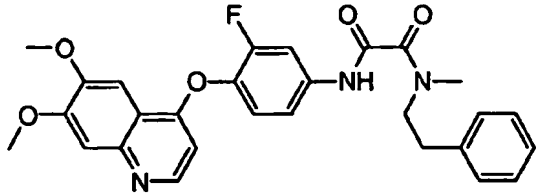
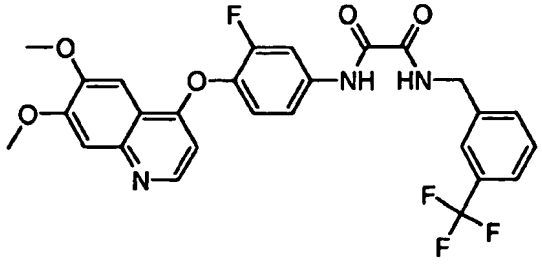
Entry	Name	Structure
72	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(1-methylpyrrolidin-2-yl)ethyl]ethanediamide	
73	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-(phenyloxy)ethyl]ethanediamide	
74	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[2-hydroxy-1-(phenylmethyl)ethyl]urea	
75	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one	
76	N'-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N-methyl-N-(2-phenylethyl)ethanediamide	
77	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{[3-(trifluoromethyl)phenyl]methyl}ethanediamide	

Table 4

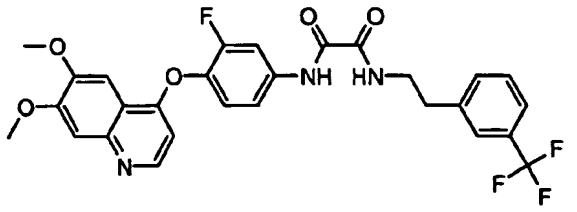
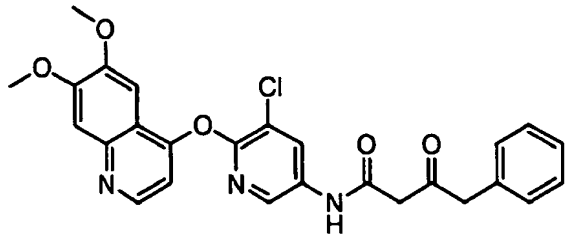
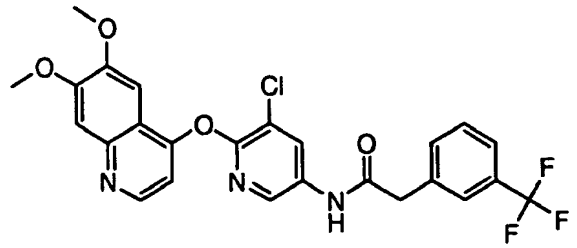
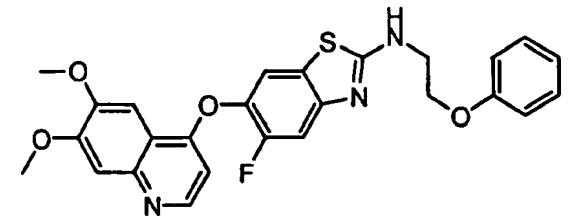
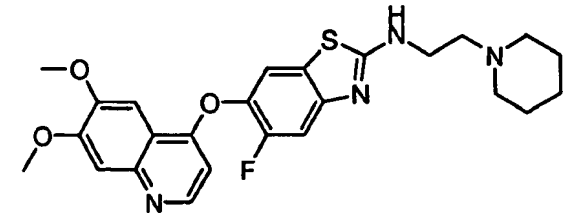
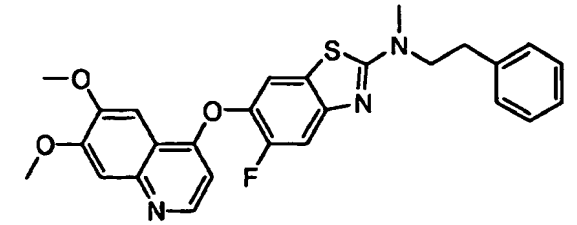
Entry	Name	Structure
78	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-{2-[3-(trifluoromethyl)phenyl]ethyl}ethanediamide	
79	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-3-oxo-4-phenylbutanamide	
80	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-2-[3-(trifluoromethyl)phenyl]acetamide	
81	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-[2-(phenyloxy)ethyl]-1,3-benzothiazol-2-amine	
82	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-(2-piperidin-1-ylethyl)-1,3-benzothiazol-2-amine	
83	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-methyl-N-(2-phenylethyl)-1,3-benzothiazol-2-amine	

Table 4

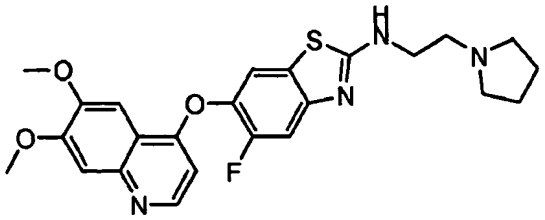
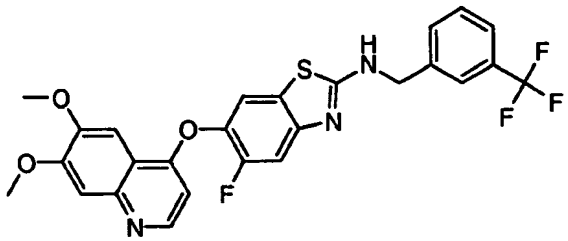
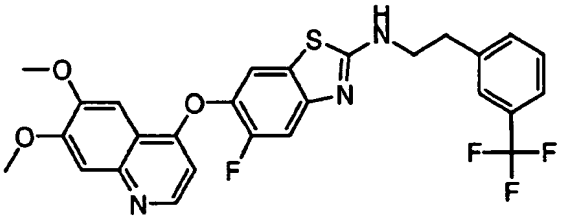
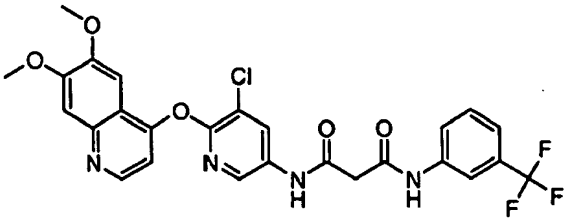
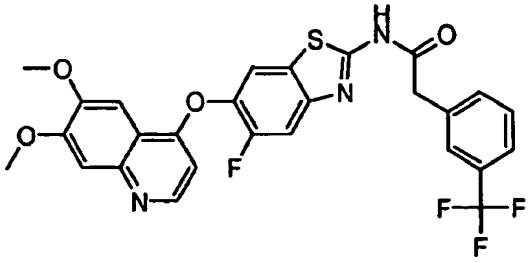
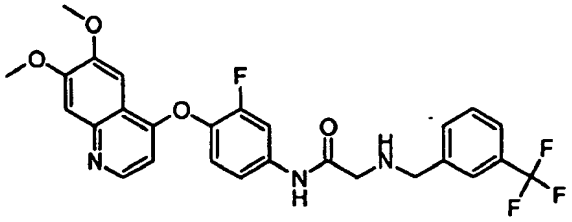
Entry	Name	Structure
84	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-(2-pyrrolidin-1-ylethyl)-1,3-benzothiazol-2-amine	
85	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-{[3-(trifluoromethyl)phenyl]methyl}-1,3-benzothiazol-2-amine	
86	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-N-{2-[3-(trifluoromethyl)phenyl]ethyl}-1,3-benzothiazol-2-amine	
87	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-[3-(trifluoromethyl)phenyl]propanediamide	
88	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3-(trifluoromethyl)phenyl]acetamide	
89	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-{[3-(trifluoromethyl)phenyl]methyl}glycinamide	

Table 4

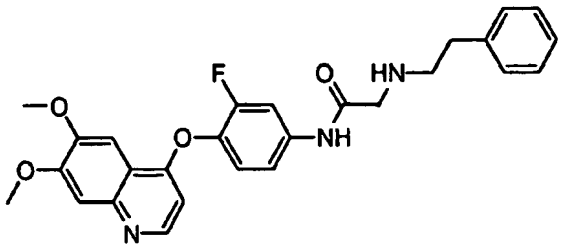
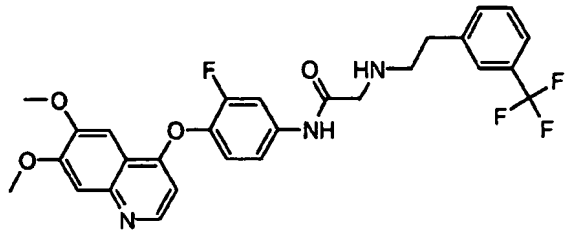
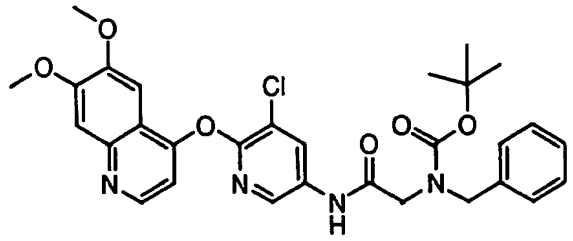
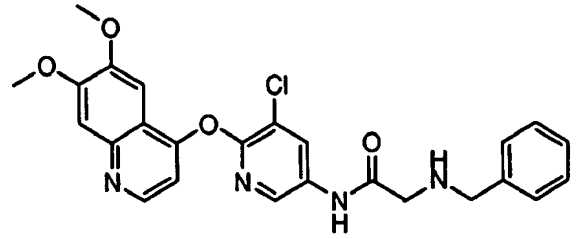
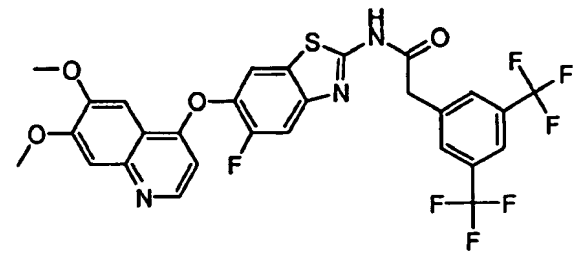
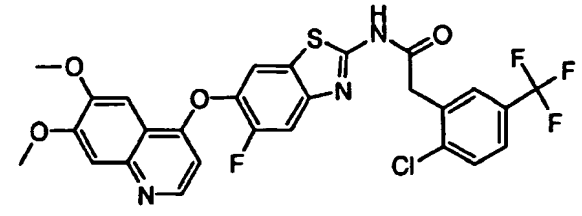
Entry	Name	Structure
90	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-(2-phenylethyl)glycinamide	
91	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-{2-[3-(trifluoromethyl)phenyl]ethyl}glycinamide	
92	benzyl-{[5-chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-ylcarbamoyl]-methyl}-carbamic acid tert-butyl ester	
93	N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N2-(phenylmethyl)glycinamide	
94	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3,5-bis(trifluoromethyl)phenyl]acetamide	
95	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[2-chloro-5-(trifluoromethyl)phenyl]acetamide	

Table 4

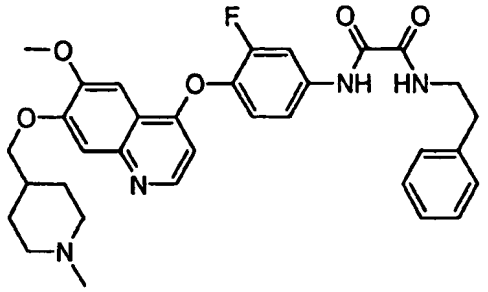
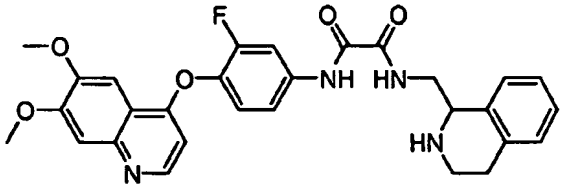
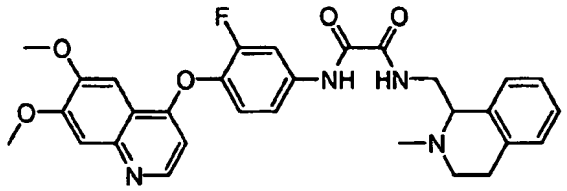
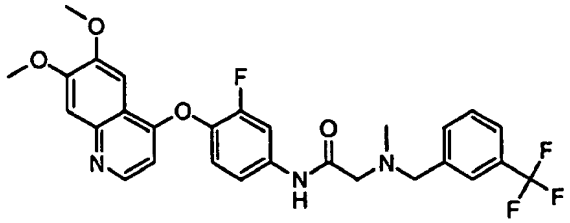
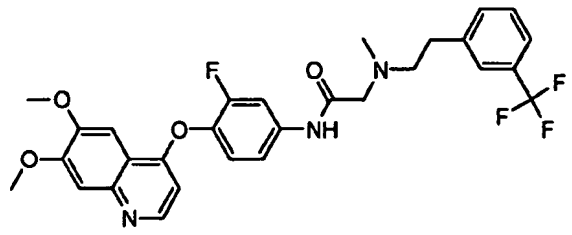
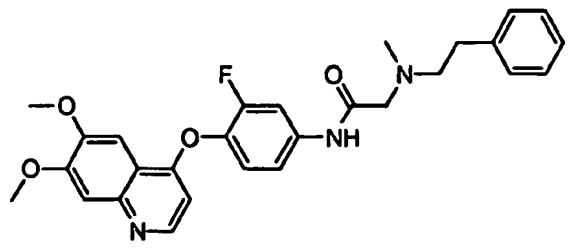
Entry	Name	Structure
96	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-N'-(2-phenylethyl)ethanediamide	
97	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)ethanediamide	
98	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]ethanediamide	
99	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-{[3-(trifluoromethyl)phenyl]methyl}glycinamide	
100	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-{2-[3-(trifluoromethyl)phenyl]ethyl}glycinamide	
101	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N2-methyl-N2-(2-phenylethyl)glycinamide	

Table 4

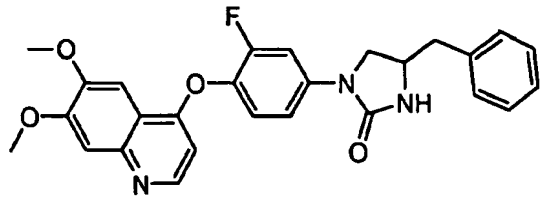
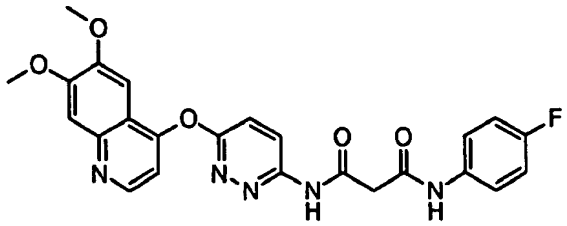
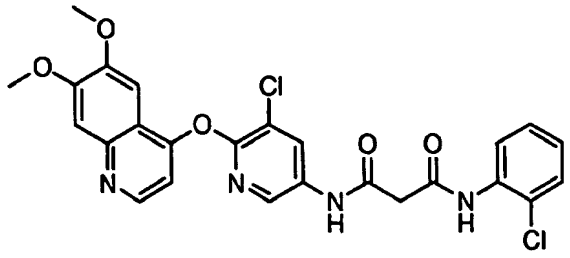
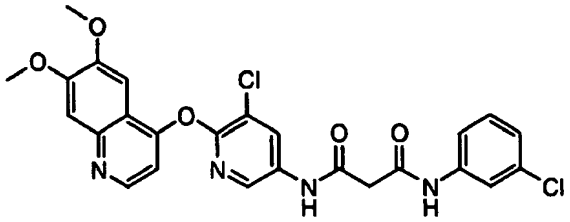
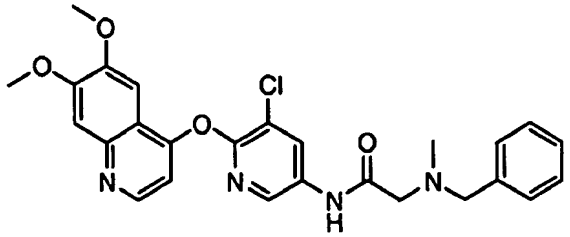
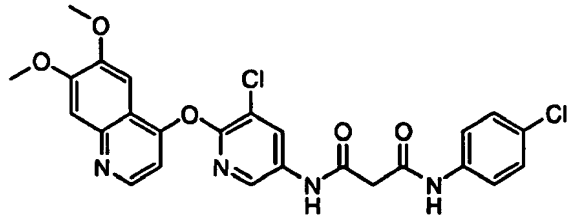
Entry	Name	Structure
102	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-4-(phenylmethyl)imidazolidin-2-one	
103	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridazin-3-yl)-N'-(4-fluorophenyl)propanediamide	
104	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-chlorophenyl)propanediamide	
105	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(3-chlorophenyl)propanediamide	
106	N1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N2-methyl-N2-(phenylmethyl)glycinamide	
107	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-chlorophenyl)propanediamide	

Table 4

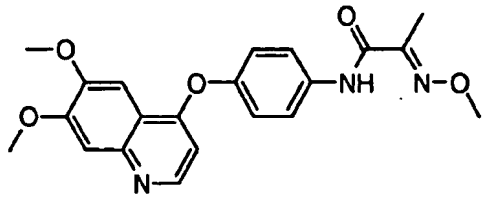
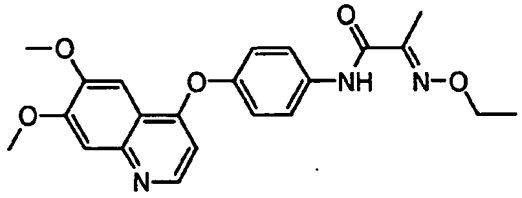
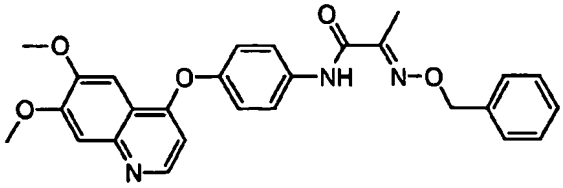
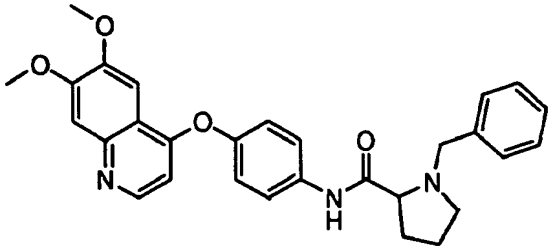
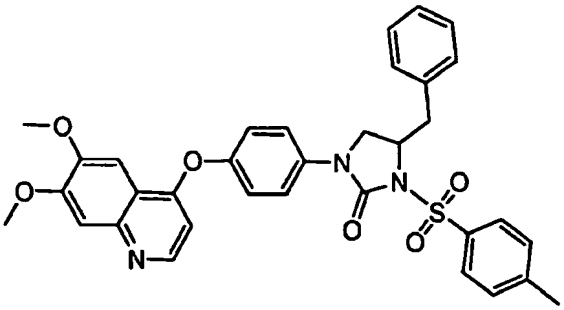
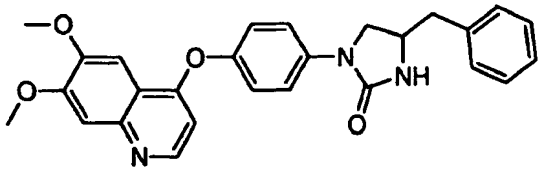
Entry	Name	Structure
108	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(methyloxy)imino]propanamide	
109	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(ethyloxy)imino]propanamide	
110	(2E)-N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-{[(phenylmethyl)oxy]imino}propanamide	
111	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-1-(phenylmethyl)prolinamide	
112	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one	
113	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)imidazolidin-2-one	

Table 4

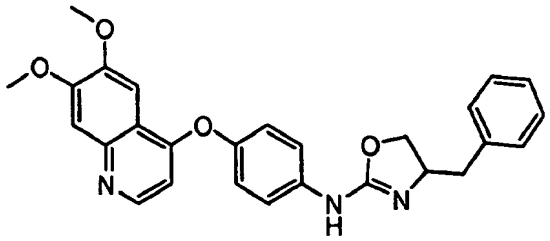
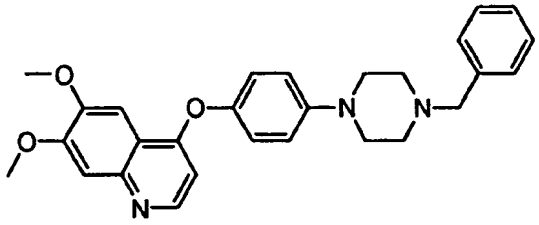
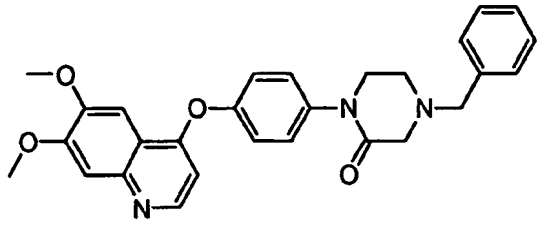
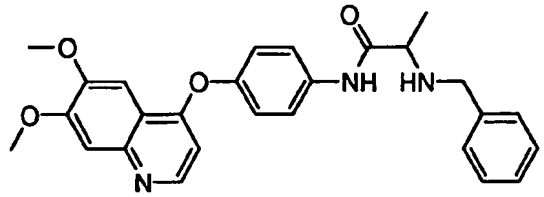
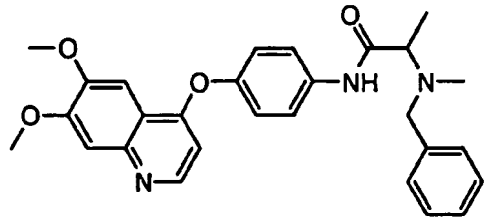
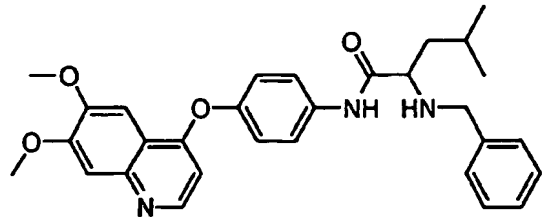
Entry	Name	Structure
114	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)-4,5-dihydro-1,3-oxazol-2-amine	
115	6,7-bis(methyloxy)-4-({4-[4-(phenylmethyl)piperazin-1-yl]phenyl}oxy)quinoline	
116	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)piperazin-2-one	
117	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-(phenylmethyl)alaninamide	
118	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-methyl-N2-(phenylmethyl)alaninamide	
119	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-(phenylmethyl)leucinamide	

Table 4

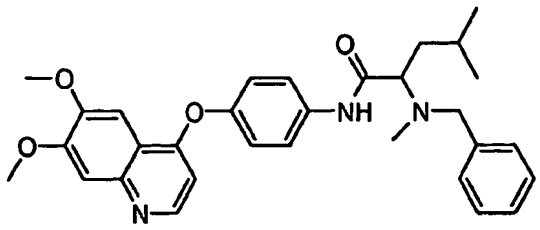
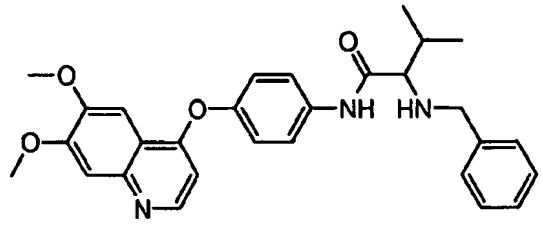
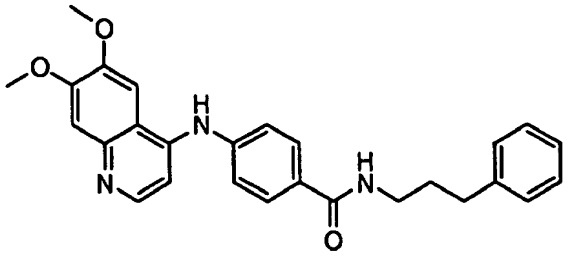
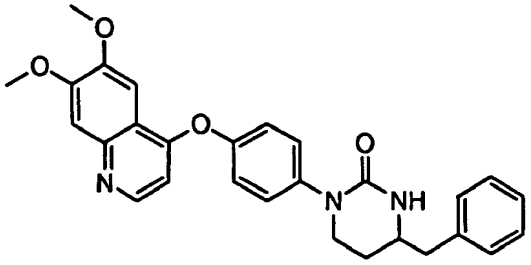
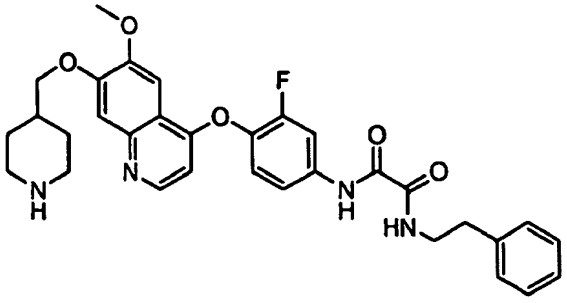
Entry	Name	Structure
120	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-methyl-N2-(phenylmethyl)leucinamide	
121	N1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N2-(phenylmethyl)valinamide	
122	4-(6,7-dimethoxy-quinolin-4-ylamino)-N-(3-phenyl-propyl)-benzamide	
123	4-benzyl-1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-tetrahydro-pyrimidin-2-one	
124	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	

Table 4

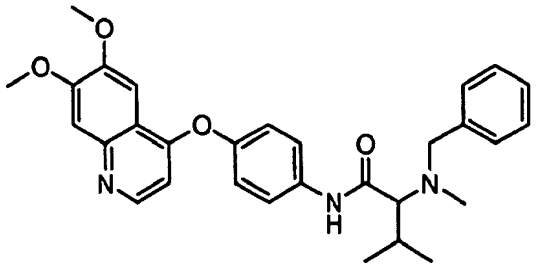
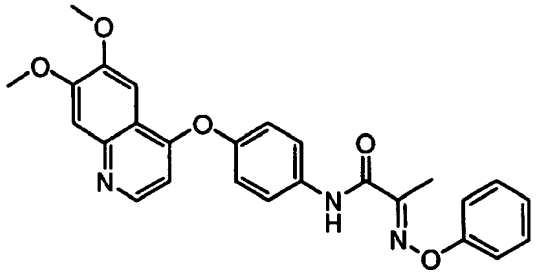
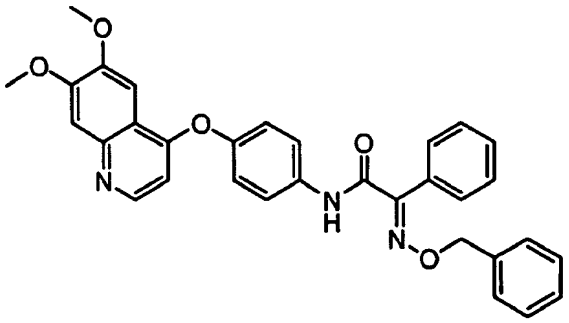
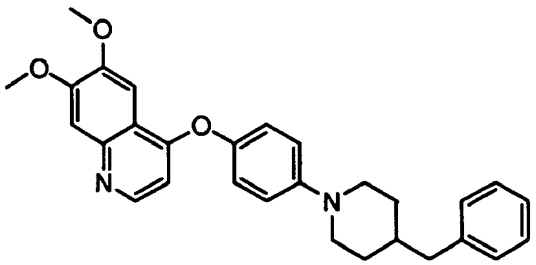
Entry	Name	Structure
127	2-(Benzyl-methyl-amino)-N-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-3-methyl-butyramide (note: Alphabetic order of prefixes ignored while selecting parent chain)	
128	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenyl]-2-phenoxyimino-propionamide	
129	2-Benzyloxyimino-N-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-2-phenyl-acetamide	
130	4-[4-(4-Benzyl-piperidin-1-yl)-phenoxy]-6,7-dimethoxy-quinoline	

Table 4

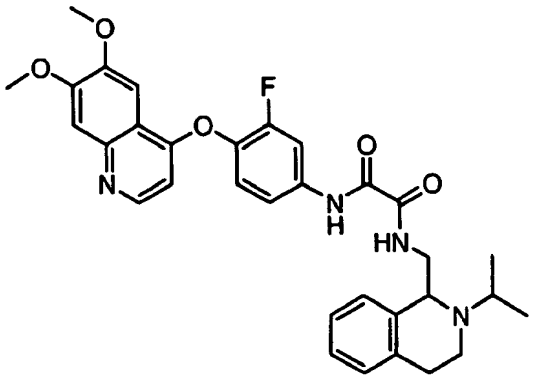
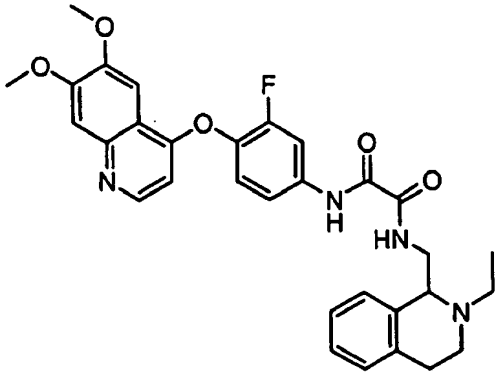
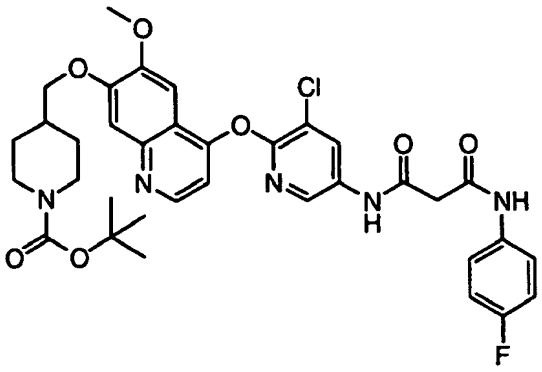
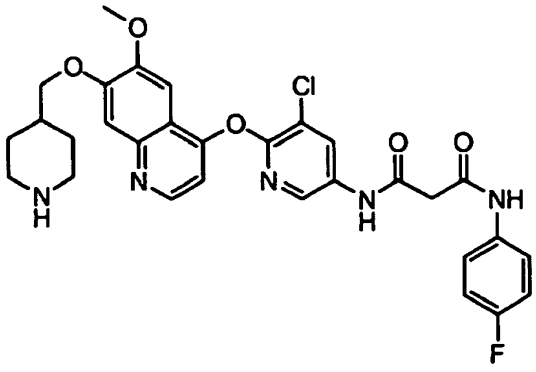
Entry	Name	Structure
131	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-oxalamide	
132	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-oxalamide	
133	4-(4-{3-Chloro-5-[2-(4-fluoro-phenylcarbamoyl)-acetylamino]-pyridin-2-yloxy}-6-methoxy-quinolin-7-yloxymethyl)-piperidine-1-carboxylic acid tert-butyl ester	
134	N-{5-Chloro-6-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	

Table 4

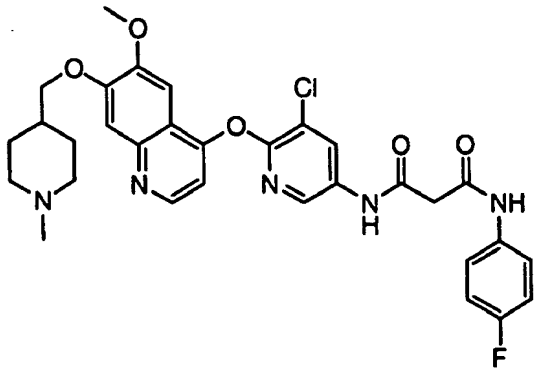
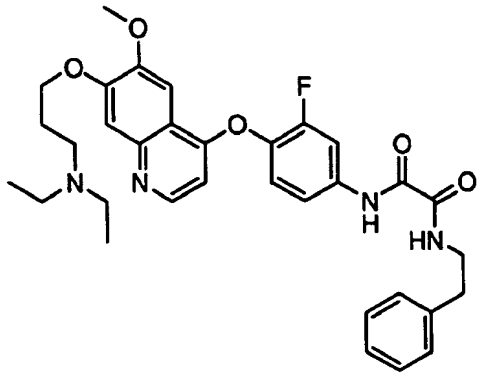
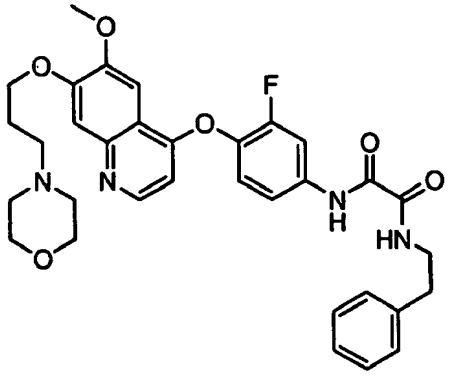
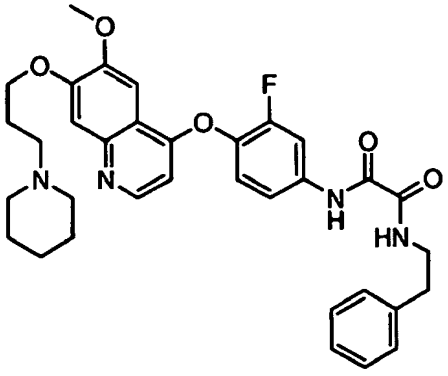
Entry	Name	Structure
135	N-{5-Chloro-6-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	
136	N-{4-[7-(3-Diethylamino-propoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide	
137	N-{3-Fluoro-4-[6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
138	N-{3-Fluoro-4-[6-methoxy-7-(3-piperidin-1-yl-propoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	

Table 4

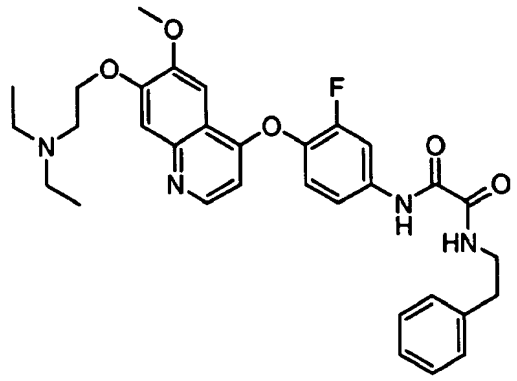
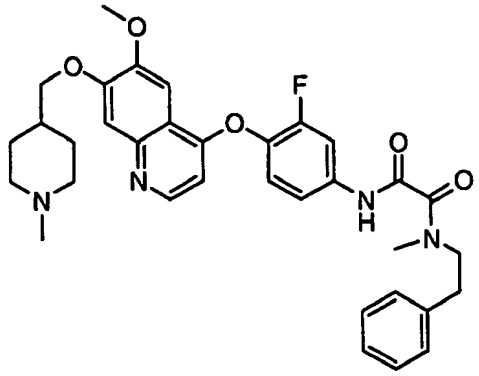
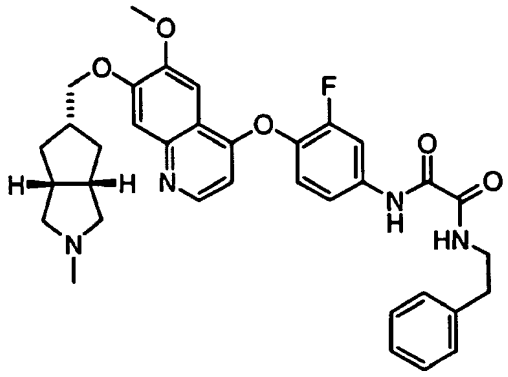
Entry	Name	Structure
139	N-{4-[7-(2-Diethylamino-ethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide	
140	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-methyl-N'-phenethyl-oxalamide	
141	N-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	

Table 4

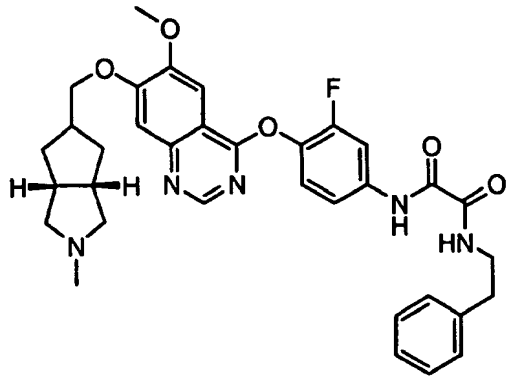
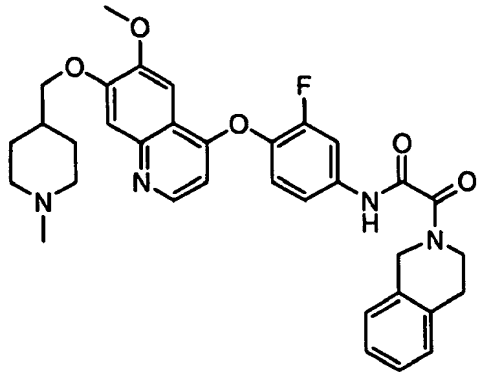
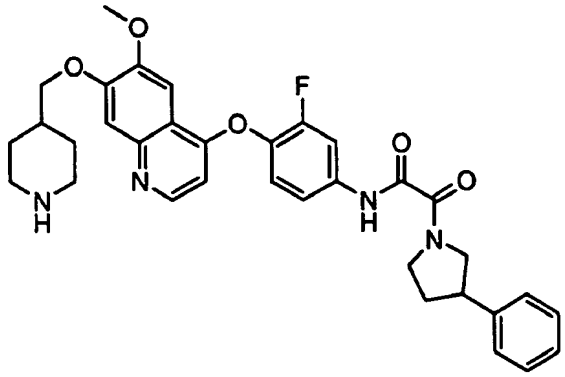
Entry	Name	Structure
142	N-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
143	2-(3,4-Dihydro-1H-isoquinolin-2-yl)-N-{3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-acetamide	
144	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-(3-phenyl-pyrrolidin-1-yl)-acetamide	

Table 4

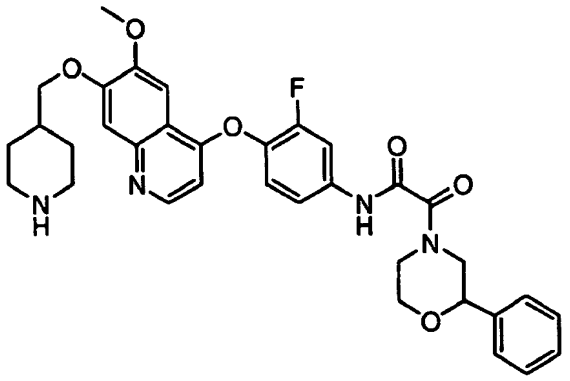
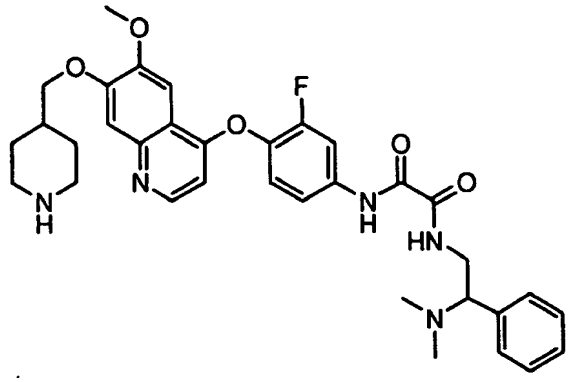
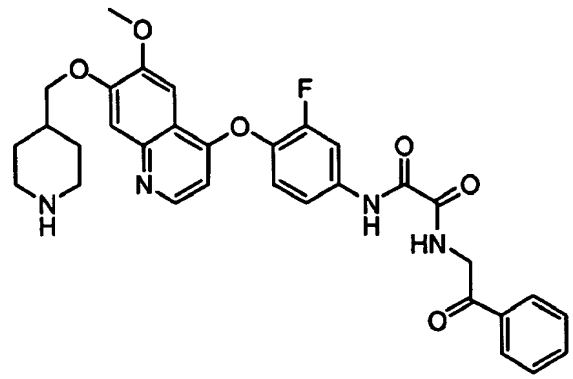
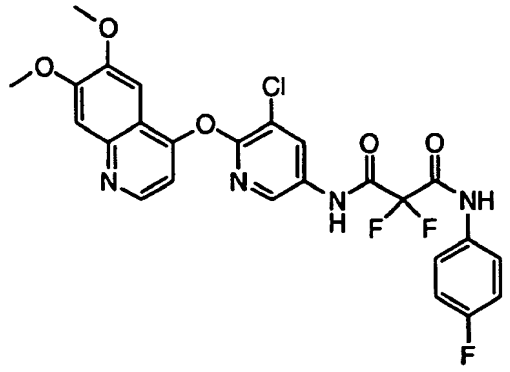
Entry	Name	Structure
145	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-(2-phenyl-morpholin-4-yl)-acetamide	
146	N-(2-Dimethylamino-2-phenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
147	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-oxo-2-phenyl-ethyl)-oxalamide	
148	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-2,2-difluoro-N'-(4-fluoro-phenyl)-malonamide	

Table 4

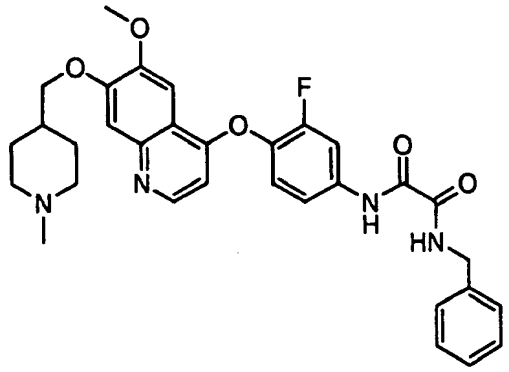
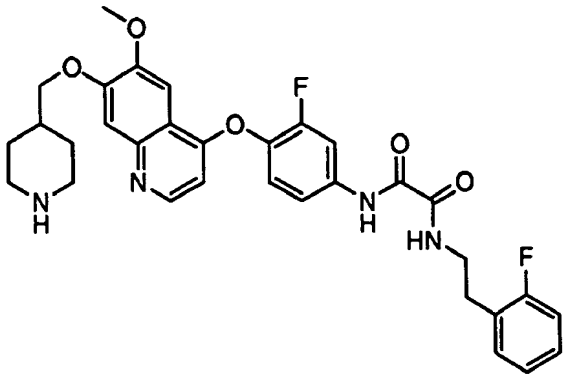
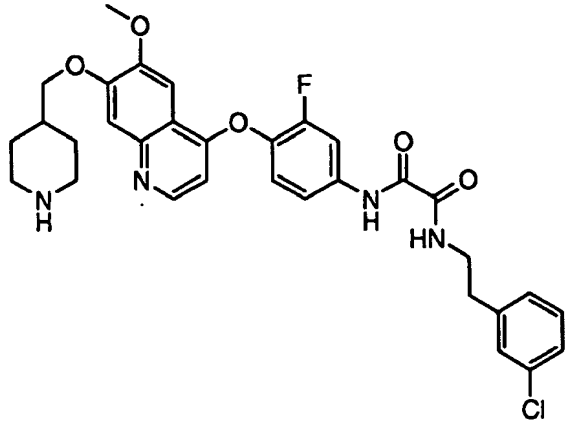
Entry	Name	Structure
149	N-Benzyl-N'-{3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
150	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-fluoro-phenyl)-ethyl]-oxalamide	
151	N-[2-(3-Chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 4

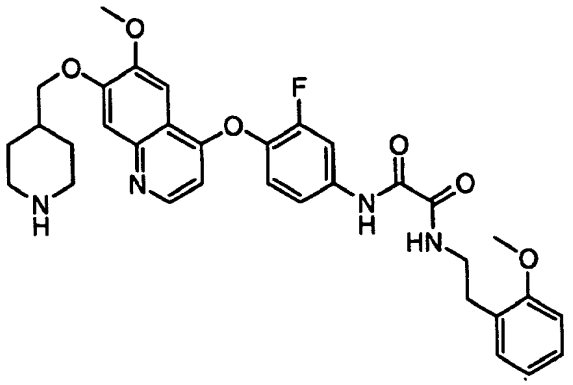
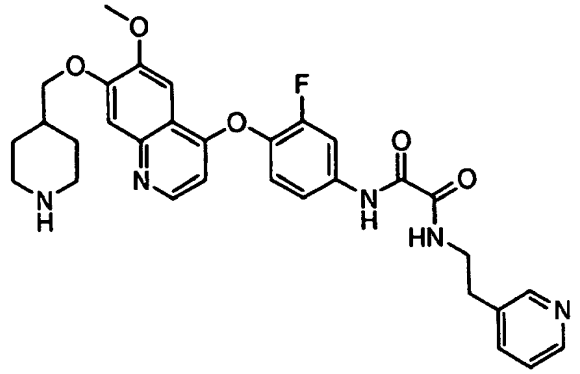
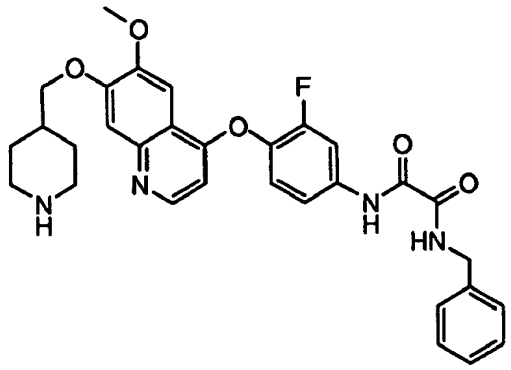
Entry	Name	Structure
152	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-methoxy-phenyl)-ethyl]-oxalamide	
153	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-3-yl-ethyl)-oxalamide	
154	N-Benzyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 4

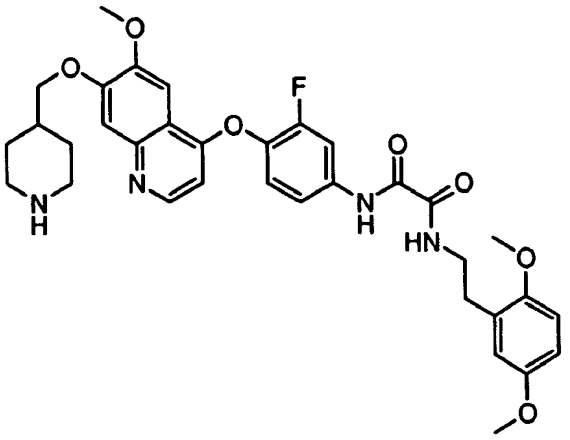
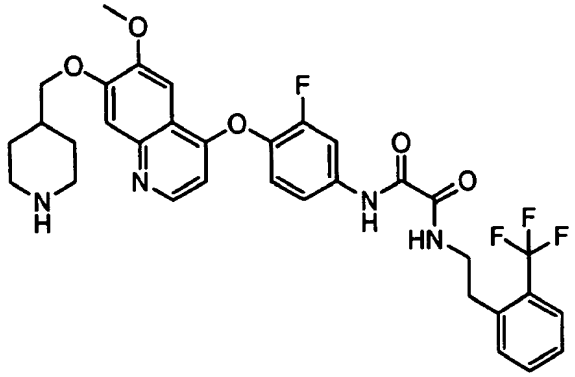
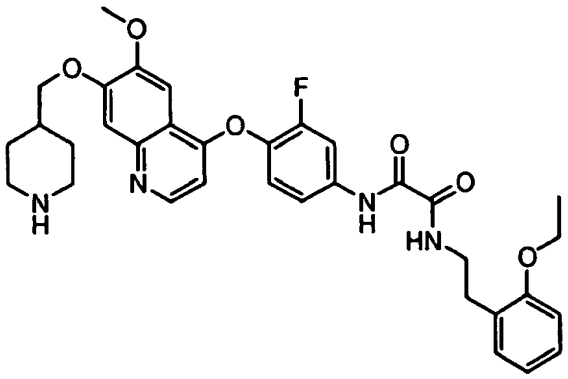
Entry	Name	Structure
155	N-[2-(2,5-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
156	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(2-trifluoromethyl-phenyl)-ethyl]-oxalamide	
157	N-[2-(2-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 4

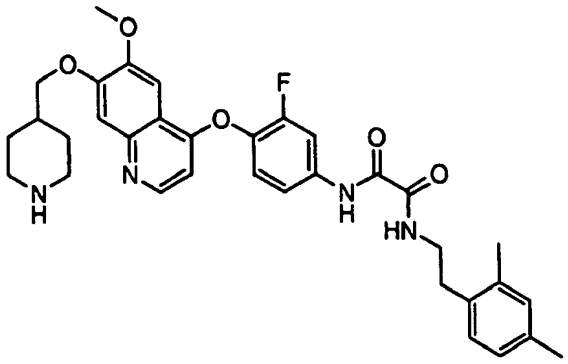
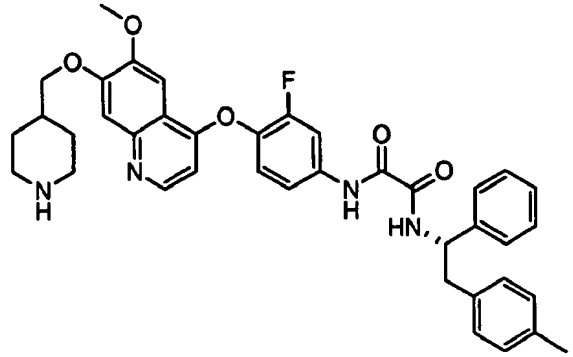
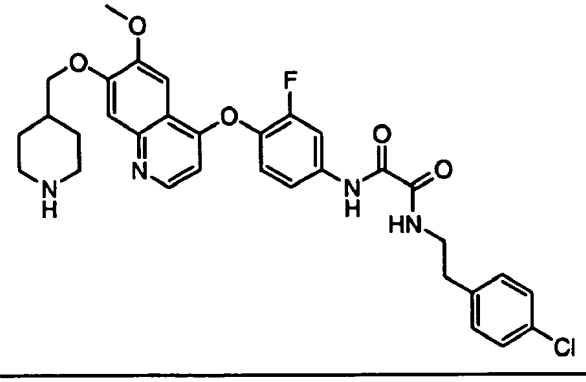
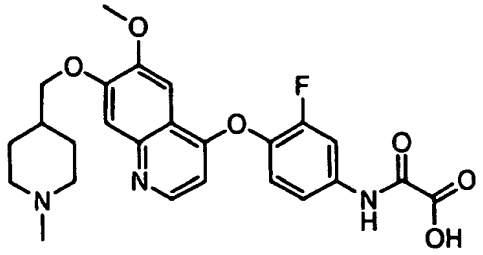
Entry	Name	Structure
158	N-[2-(2,4-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
159	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*S*-phenyl-2-p-tolyl-ethyl)-oxalamide	
160	N-[2-(4-Chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
161	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamic acid	

Table 4

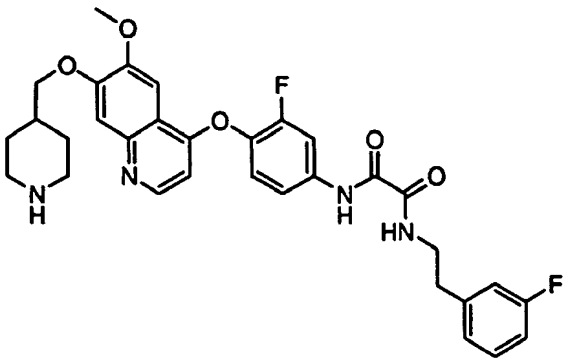
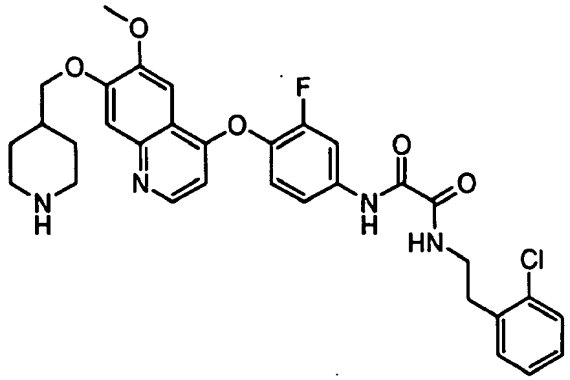
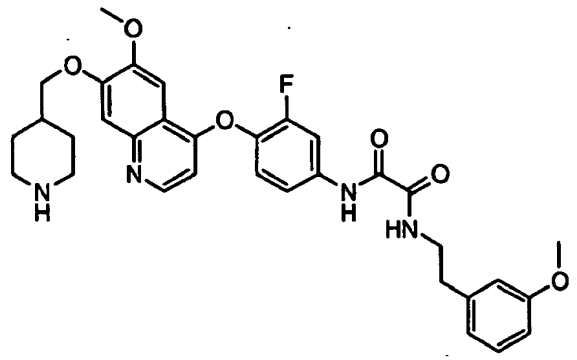
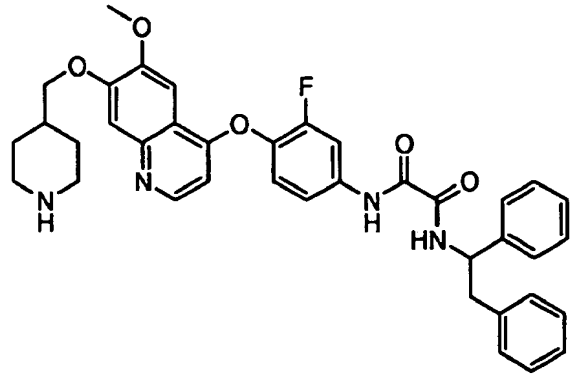
Entry	Name	Structure
162	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-fluoro-phenyl)-ethyl]-oxalamide	
163	N-[2-(2-Chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
164	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-methoxy-phenyl)-ethyl]-oxalamide	
165	N-(1,2-Diphenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 4

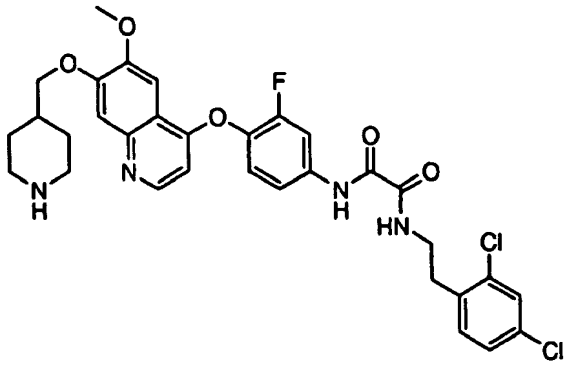
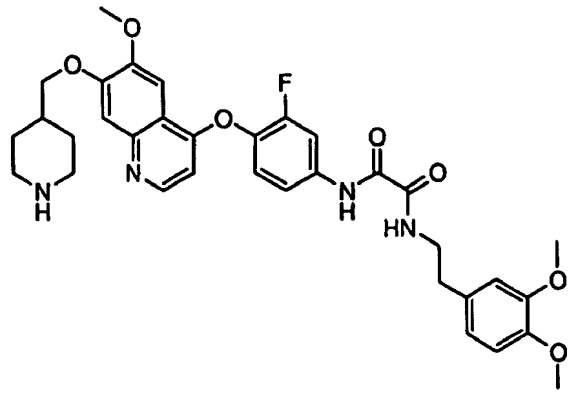
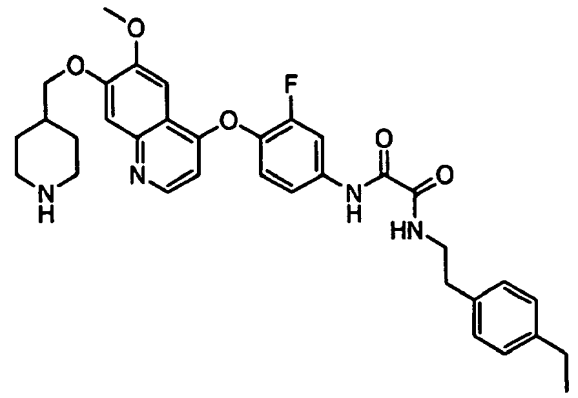
Entry	Name	Structure
166	N-[2-(2,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
167	N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
168	N-[2-(4-Ethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 4

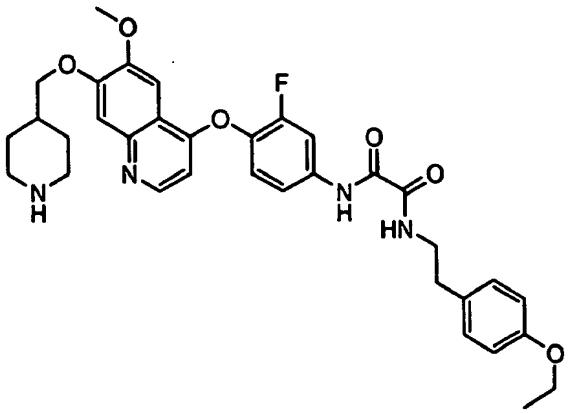
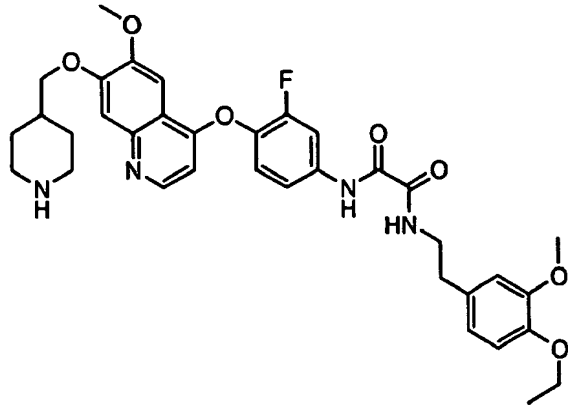
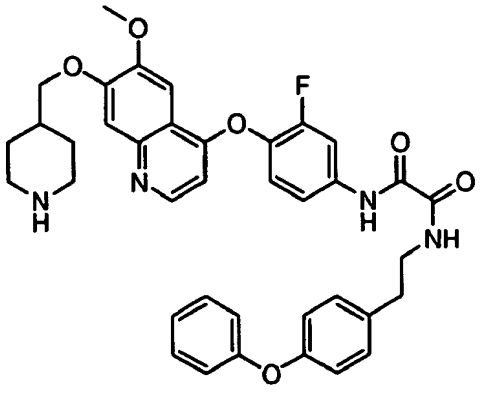
Entry	Name	Structure
169	N-[2-(4-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
170	N-[2-(4-Ethoxy-3-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
171	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-phenoxy-phenyl)-ethyl]-oxalamide	

Table 4

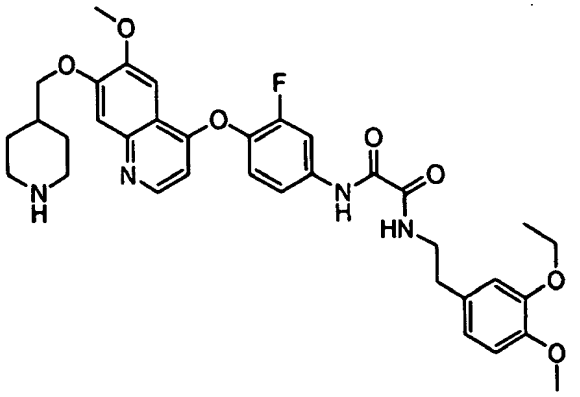
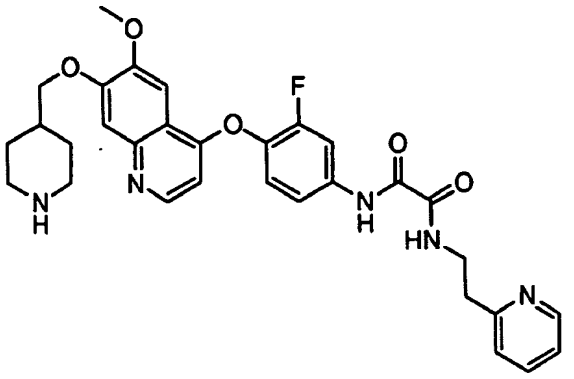
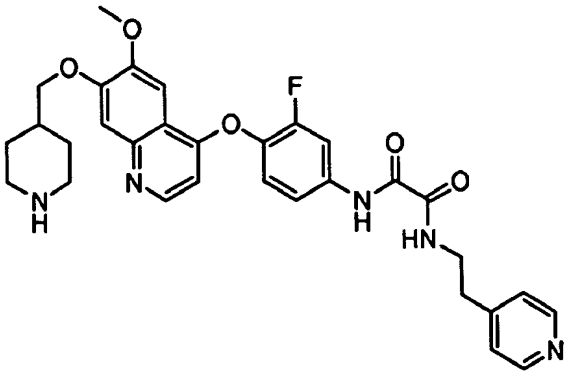
Entry	Name	Structure
172	N-[2-(3-Ethoxy-4-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
173	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-2-yl-ethyl)-oxalamide	
174	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-pyridin-4-yl-ethyl)-oxalamide	

Table 4

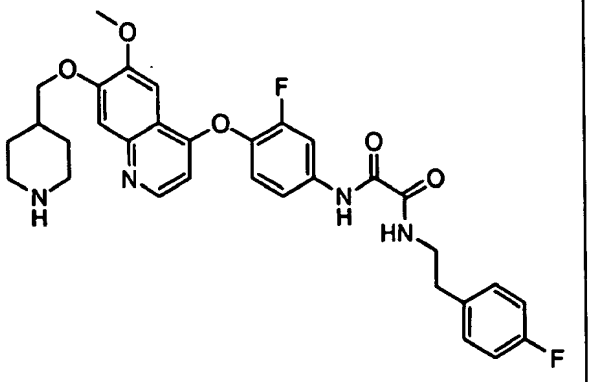
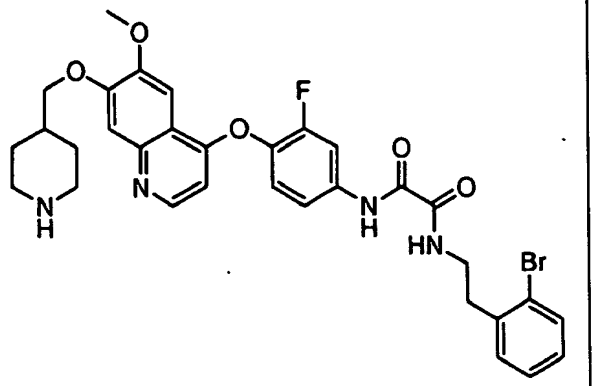
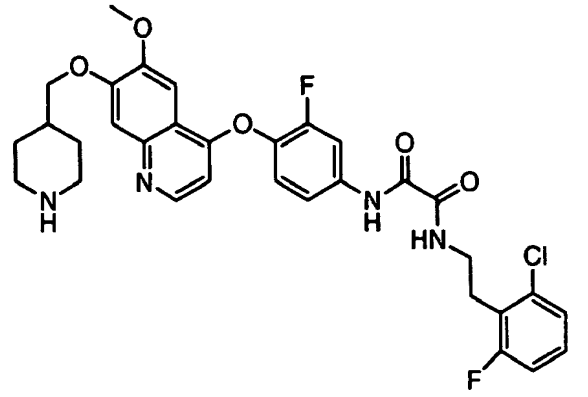
Entry	Name	Structure
175	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-fluoro-phenyl)-ethyl]-oxalamide	
176	N-[2-(2-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
177	N-[2-(2-Chloro-6-fluoro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 4

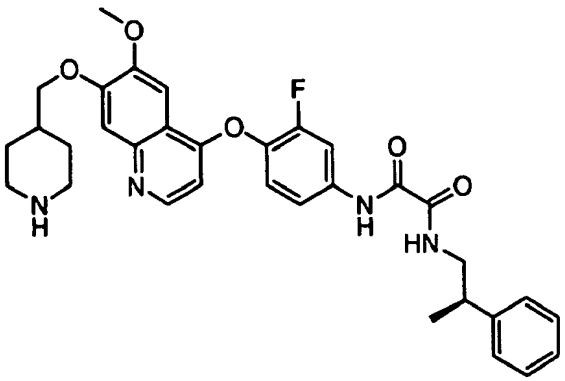
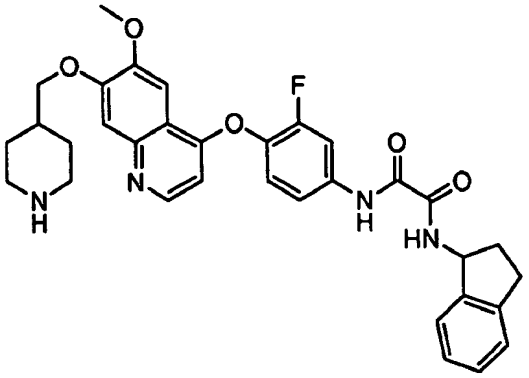
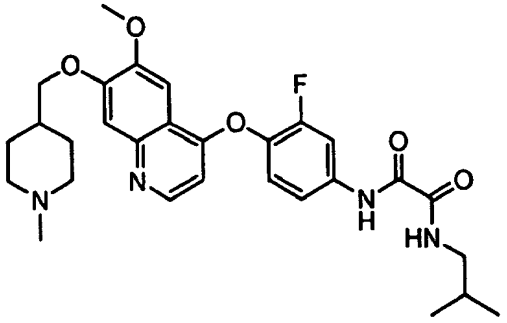
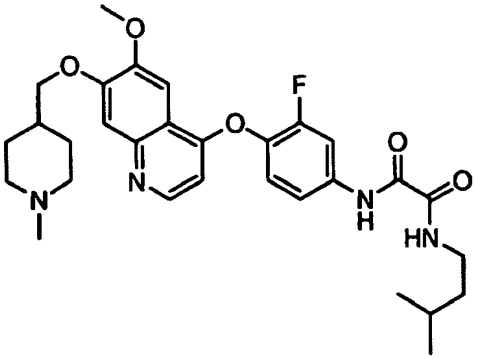
Entry	Name	Structure
178	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2*R*-phenyl-propyl)-oxalamide	
179	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-indan-1-yl-oxalamide	
180	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-isobutyl-oxalamide	
181	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-butyl)-oxalamide	

Table 4

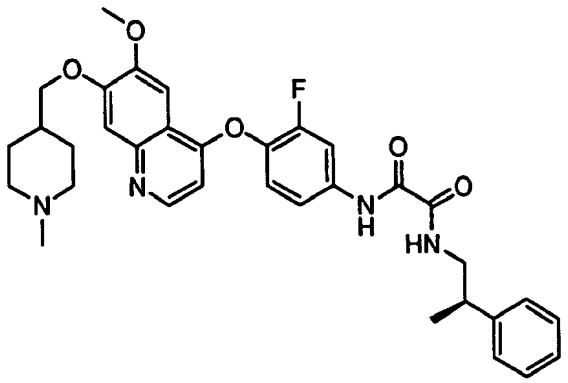
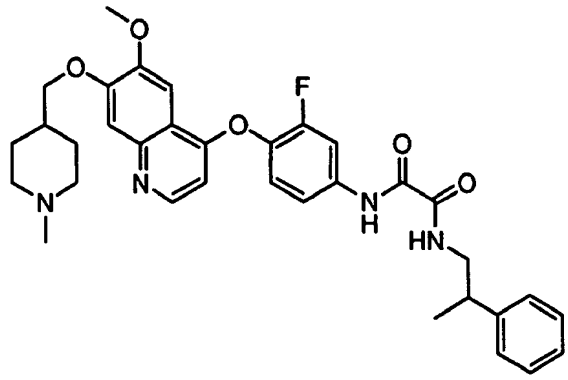
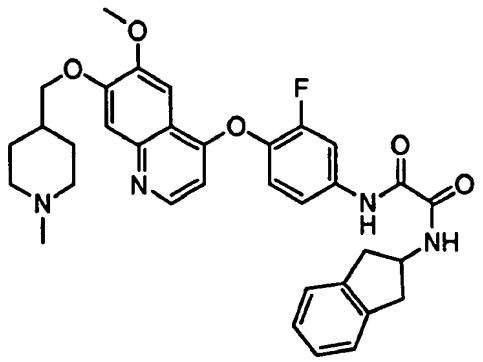
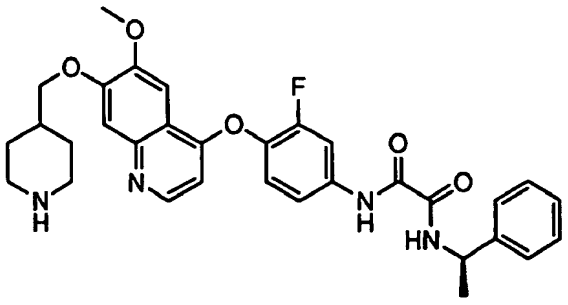
Entry	Name	Structure
182	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2*R*-phenyl-propyl)-oxalamide	
183	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-phenyl-propyl)-oxalamide	
184	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-indan-2-yl-oxalamide	
185	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*R*-phenyl-ethyl)-oxalamide	

Table 4

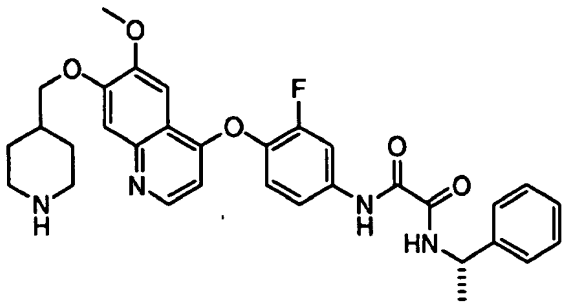
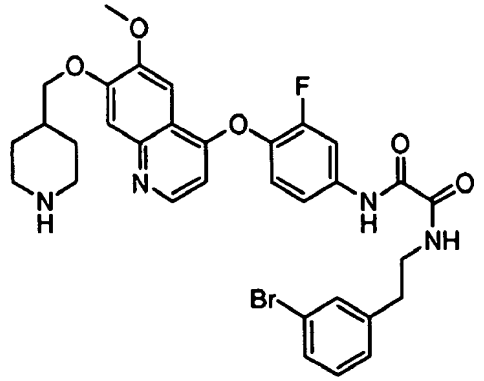
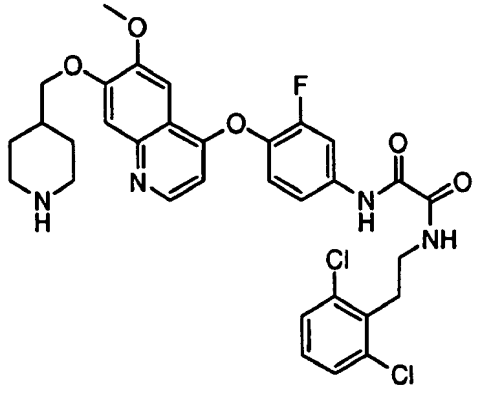
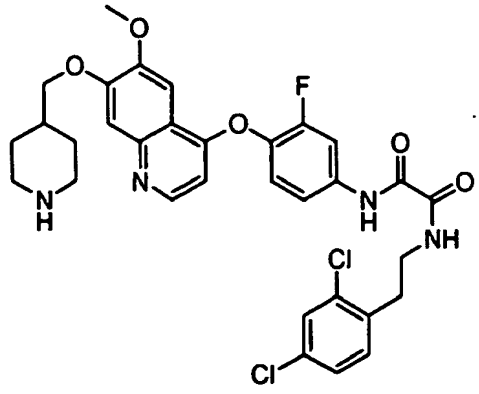
Entry	Name	Structure
186	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1*S*-phenyl-ethyl)-oxalamide	
187	N-[2-(3-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
188	N-[2-(2,6-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
189	N-[2-(2,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 4

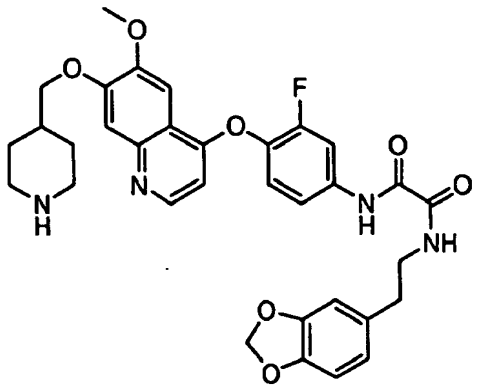
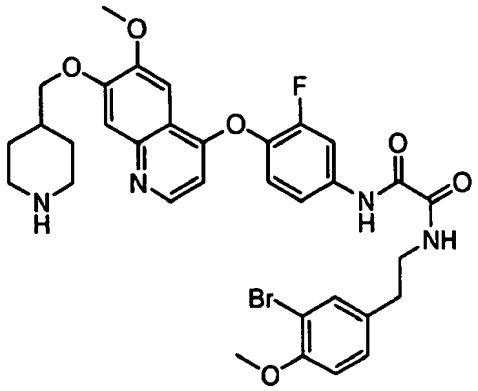
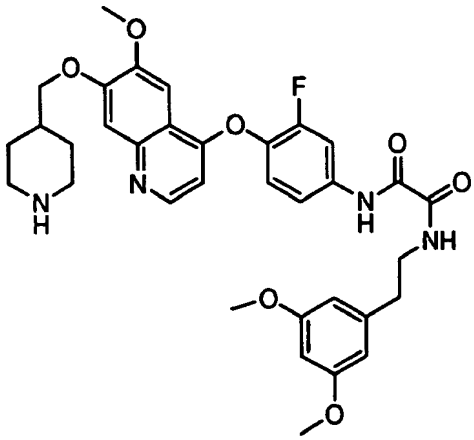
Entry	Name	Structure
190	N-(2-Benzo[1,3]dioxol-5-yl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
192	N-[2-(3-Bromo-4-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
193	N-[2-(3,5-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 4

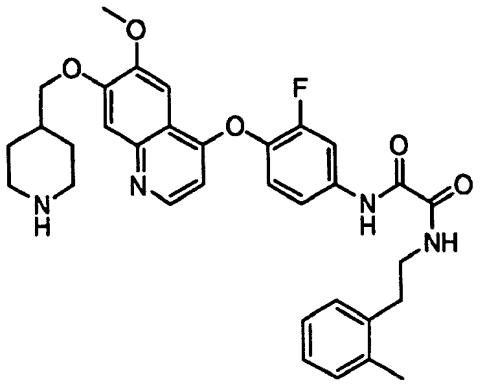
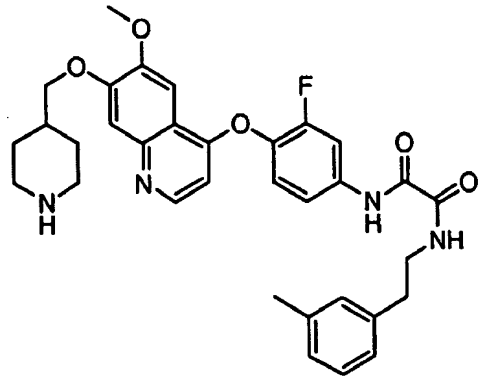
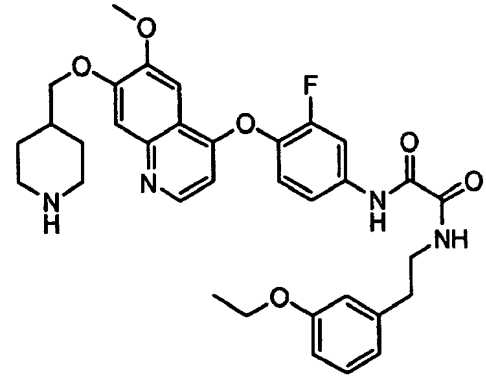
Entry	Name	Structure
194	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-o-tolyl-ethyl)-oxalamide	
195	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-m-tolyl-ethyl)-oxalamide	
196	N-[2-(3-Ethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 4

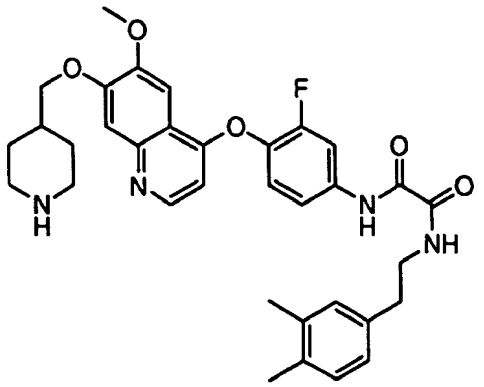
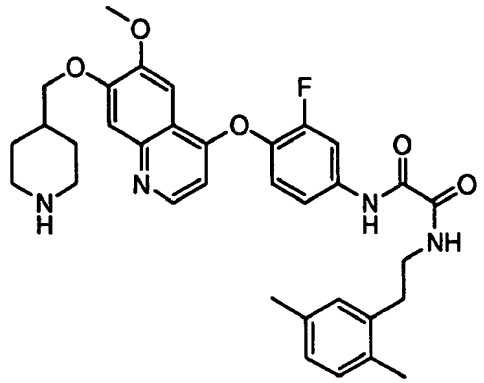
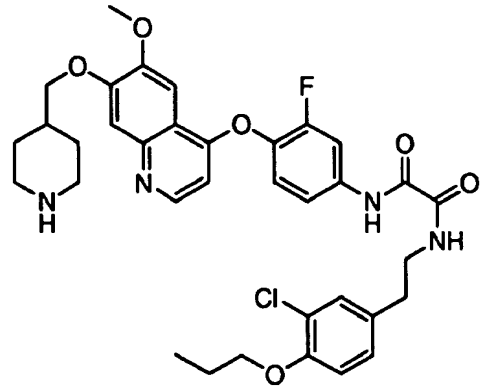
Entry	Name	Structure
197	N-[2-(3,4-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
198	N-[2-(2,5-Dimethyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
199	N-[2-(3-Chloro-4-propoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 4

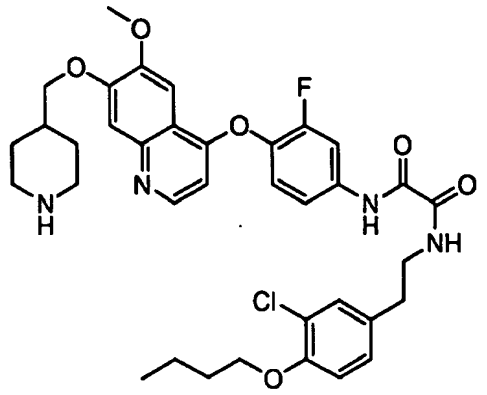
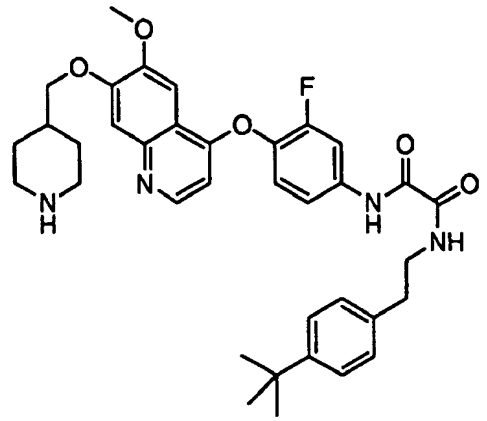
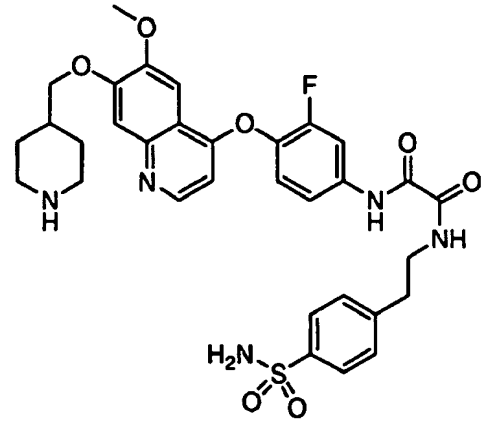
Entry	Name	Structure
200	N-[2-(4-Butoxy-3-chloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
201	N-[2-(4-tert-Butyl-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
202	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-sulfamoyl-phenyl)-ethyl]-oxalamide	

Table 4

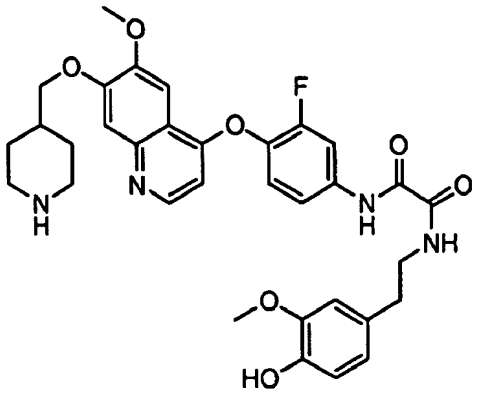
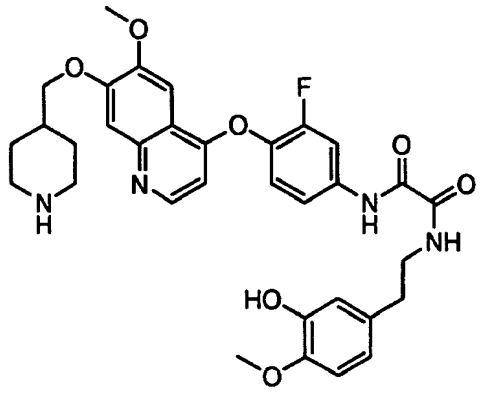
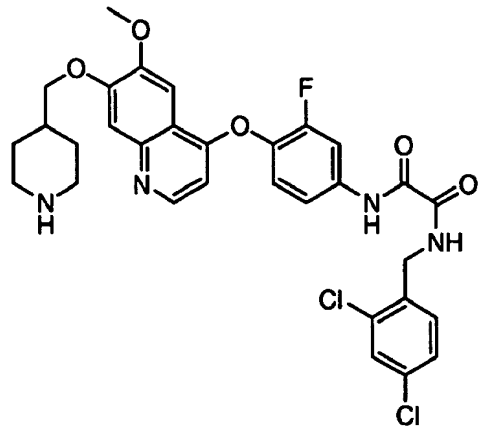
Entry	Name	Structure
203	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-hydroxy-3-methoxy-phenyl)-ethyl]-oxalamide	
204	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(3-hydroxy-4-methoxy-phenyl)-ethyl]-oxalamide	
205	N-(2,4-Dichloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 4

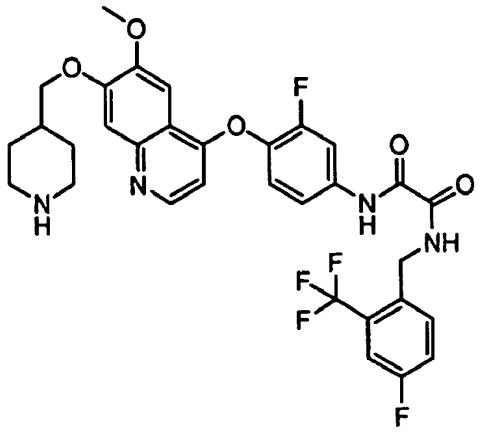
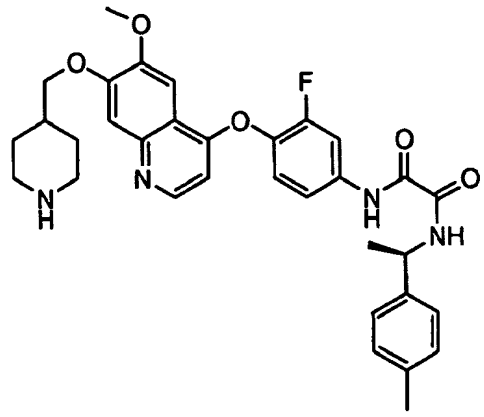
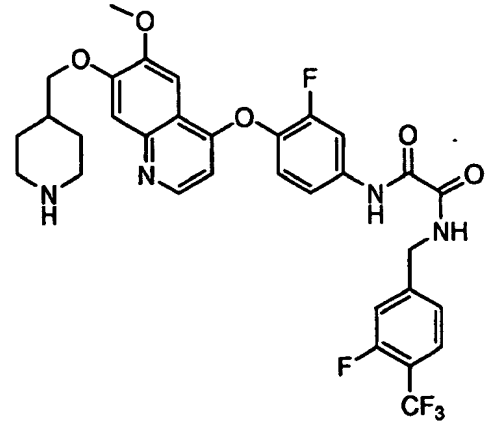
Entry	Name	Structure
206	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-fluoro-2-trifluoromethyl-benzyl)-oxalamide	
207	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-p-tolyl-ethyl)-oxalamide	
208	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-fluoro-4-trifluoromethyl-benzyl)-oxalamide	

Table 4

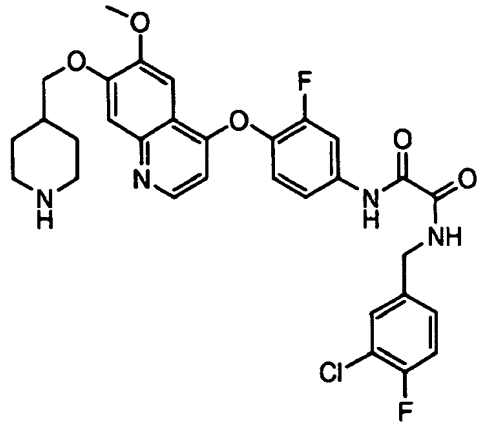
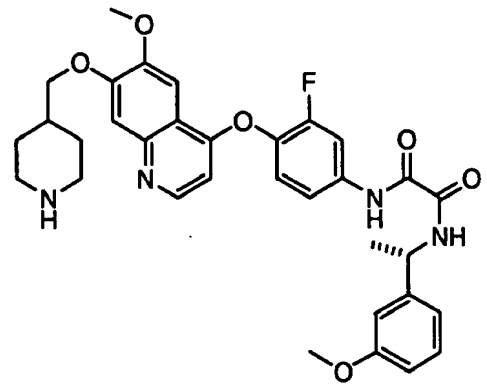
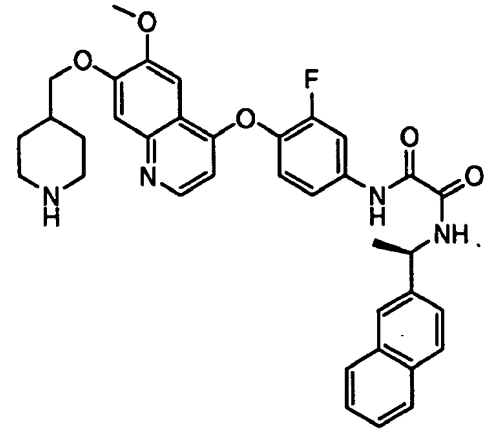
Entry	Name	Structure
209	N-(3-Chloro-4-fluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
210	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[1-(3-methoxy-phenyl)-ethyl]-oxalamide	
211	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-naphthalen-2-yl-ethyl)-oxalamide	

Table 4

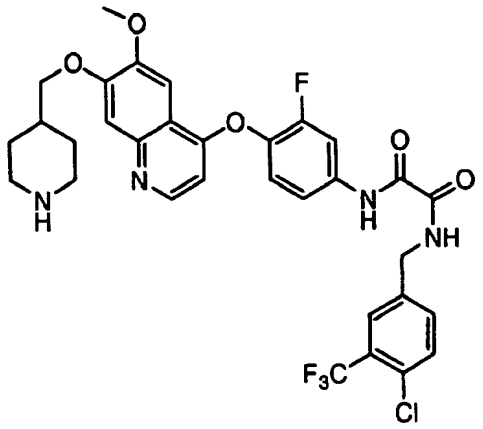
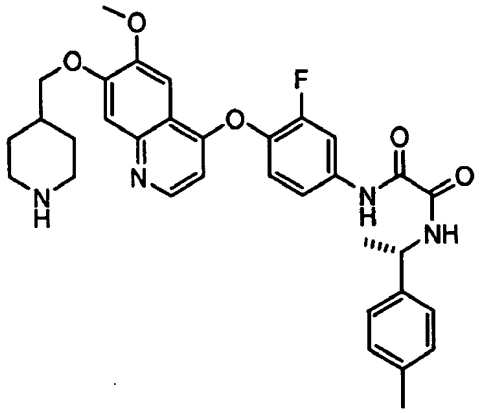
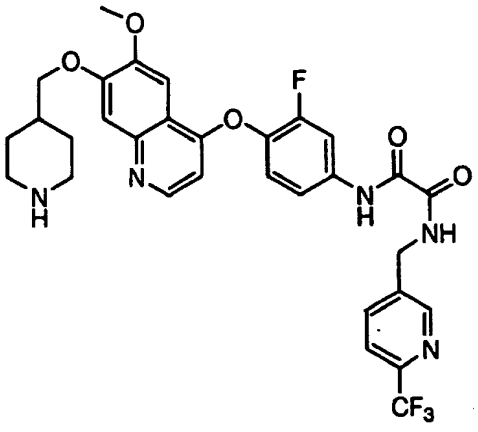
Entry	Name	Structure
212	N-(4-Chloro-3-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
213	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1-p-tolyl-ethyl)-oxalamide	
214	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(6-trifluoromethyl-pyridin-3-ylmethyl)-oxalamide	

Table 4

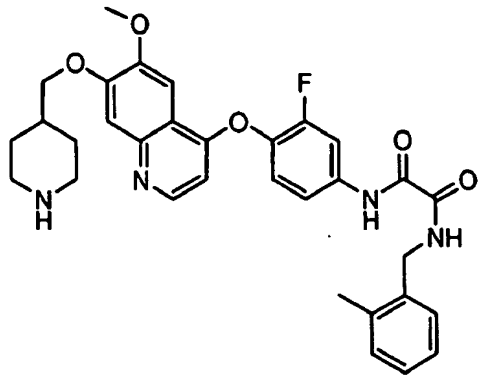
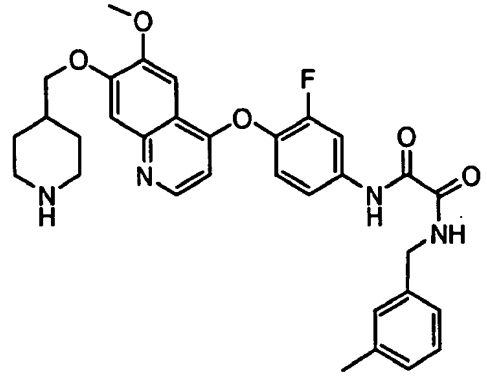
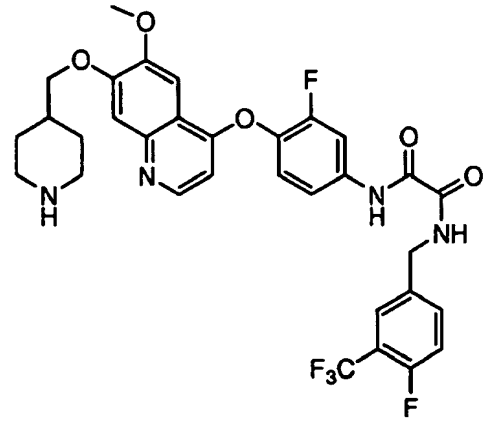
Entry	Name	Structure
215	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-methyl-benzyl)-oxalamide	
216	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-benzyl)-oxalamide	
217	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-fluoro-3-trifluoromethyl-benzyl)-oxalamide	

Table 4

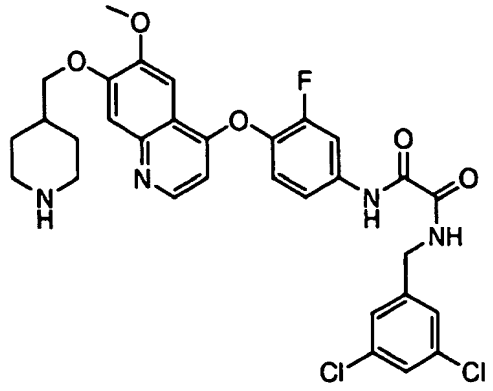
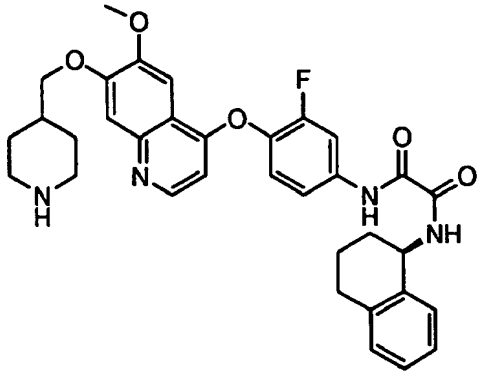
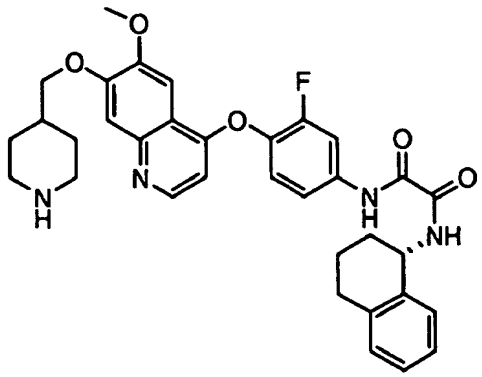
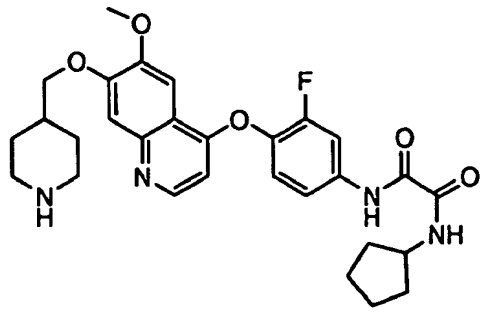
Entry	Name	Structure
218	N-(3,5-Dichloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
219	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R,2,3,4-tetrahydro-naphthalen-1-yl)-oxalamide	
220	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1S,2,3,4-tetrahydro-naphthalen-1-yl)-oxalamide	
221	N-Cyclopentyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 4

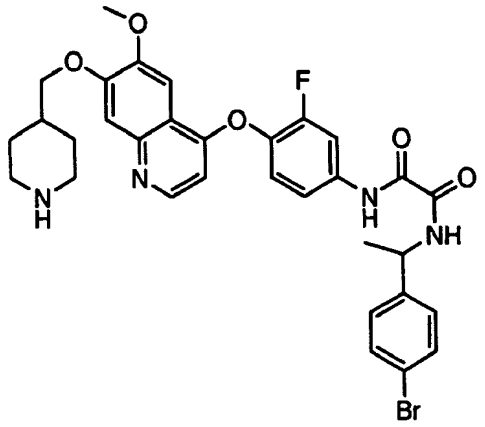
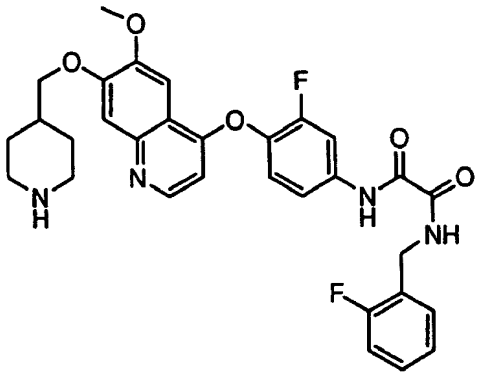
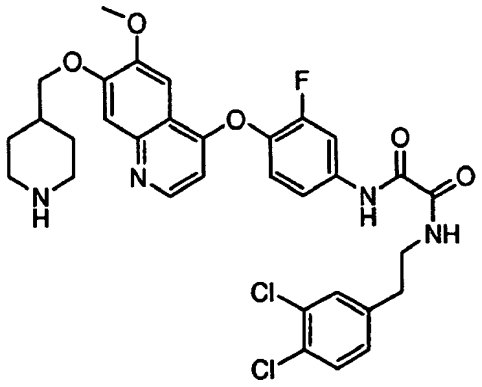
Entry	Name	Structure
222	N-[1-(4-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
223	N-(2-Fluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
224	N-[2-(3,4-Dichloro-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 4

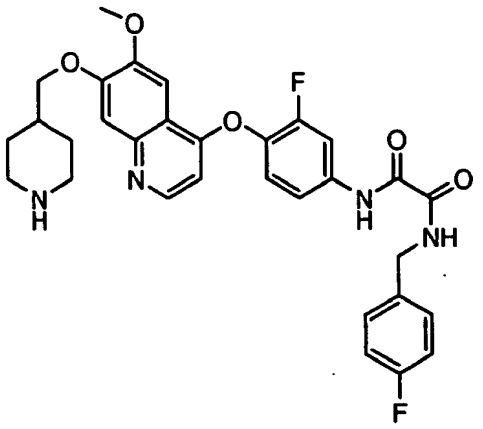
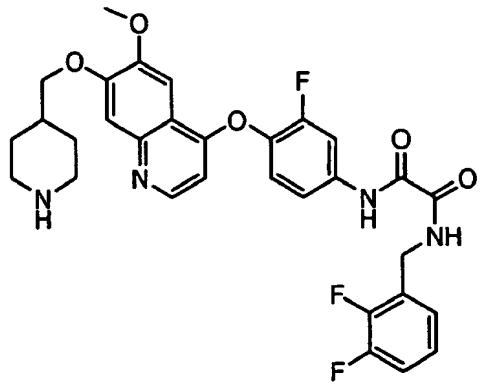
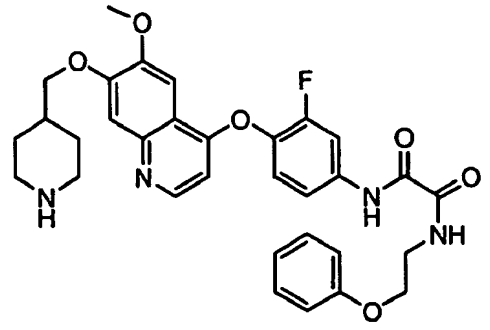
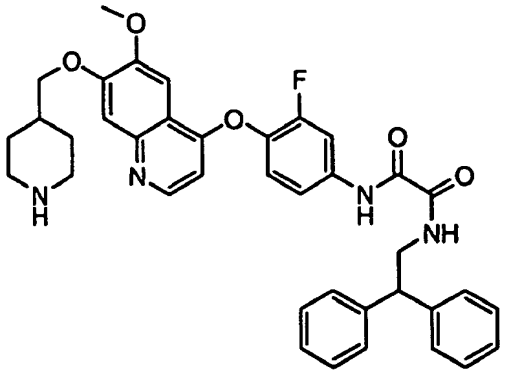
Entry	Name	Structure
225	N-(4-Fluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
226	N-(2,3-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
227	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-phenoxy-ethyl)-oxalamide	
228	N-(2,2-Diphenyl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 4

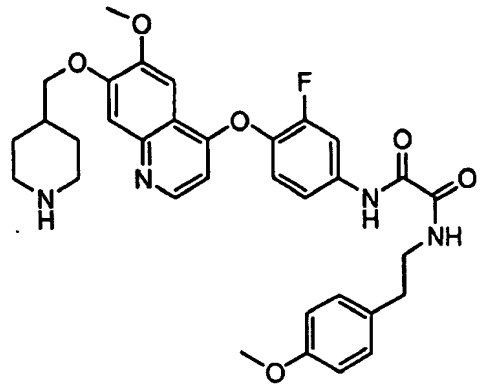
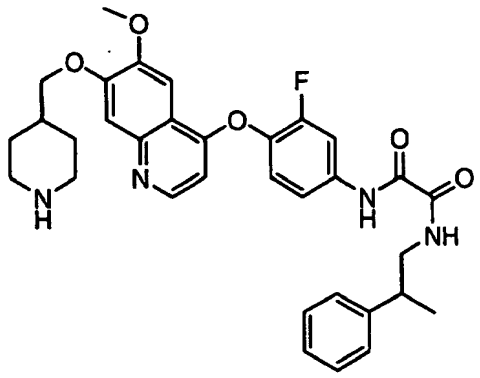
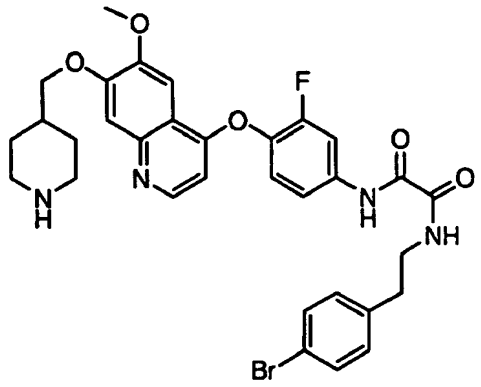
Entry	Name	Structure
229	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-methoxy-phenyl)-ethyl]-oxalamide	
230	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-phenyl-propyl)-oxalamide	
231	N-[2-(4-Bromo-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 4

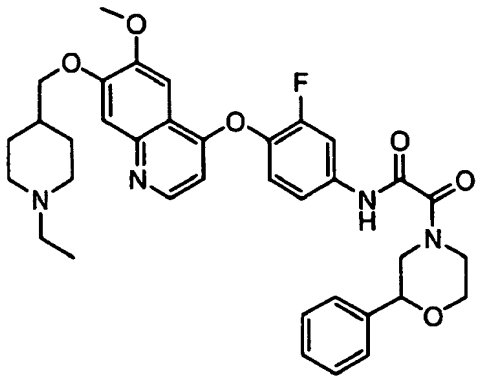
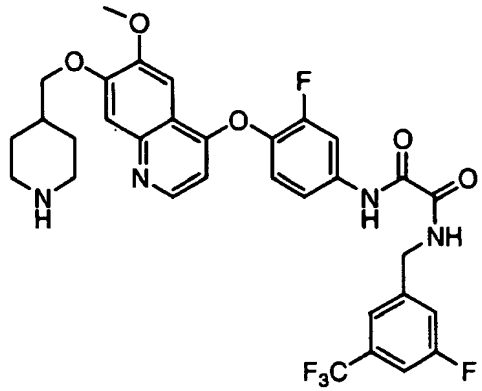
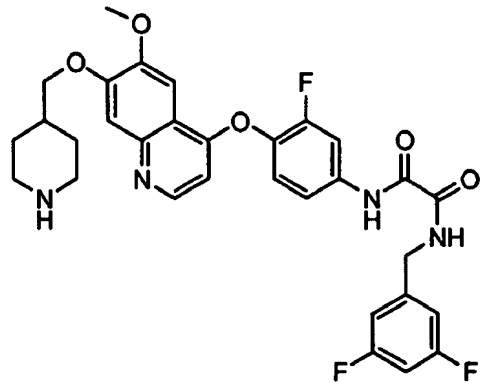
Entry	Name	Structure
232	N-{4-[7-(1-Ethyl-piperidin-4-ylmethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-2-oxo-2-(2-phenyl-morpholin-4-yl)-acetamide	
233	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-fluoro-5-trifluoromethyl-benzyl)-oxalamide	
234	N-(3,5-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 4

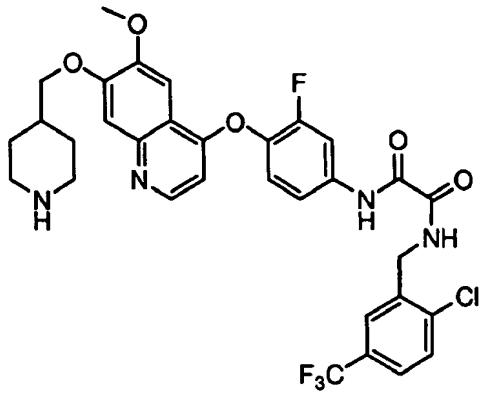
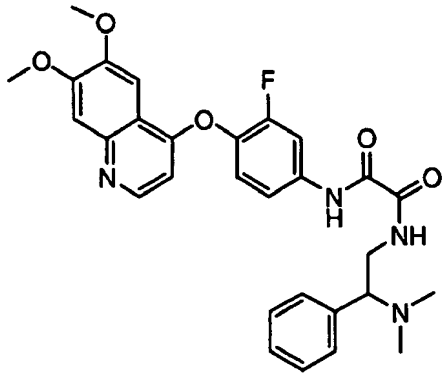
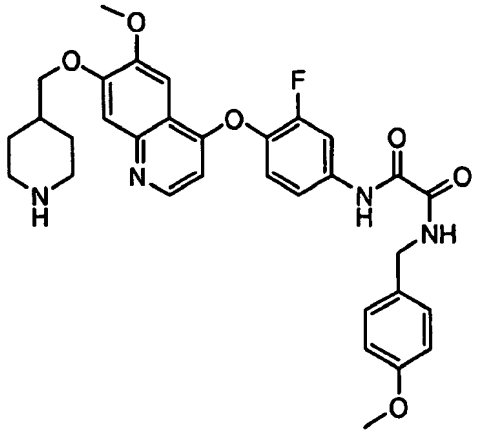
Entry	Name	Structure
235	N-(2-Chloro-5-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
236	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-N'-(2-dimethylamino-2-phenyl-ethyl)-oxalamide	
237	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-methoxy-benzyl)-oxalamide	

Table 4

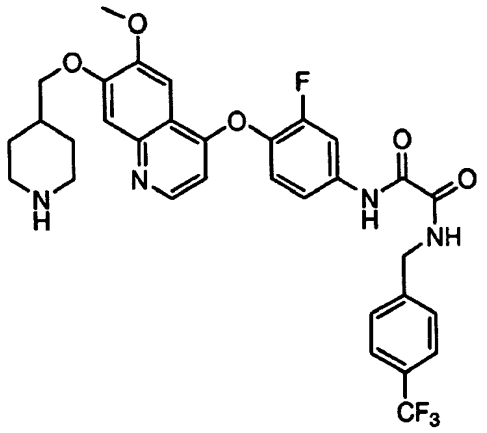
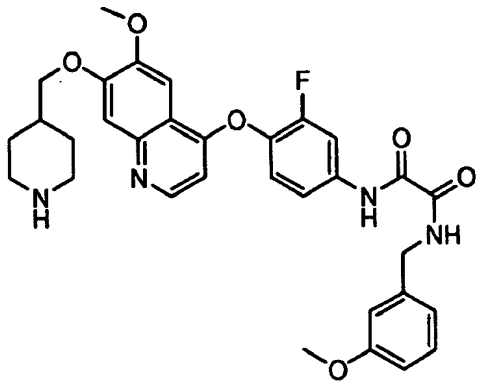
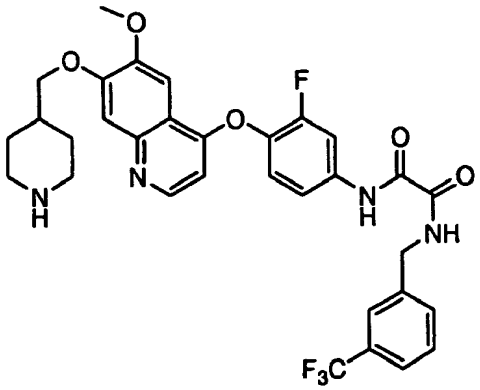
Entry	Name	Structure
238	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethyl-benzyl)-oxalamide	
239	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methoxy-benzyl)-oxalamide	
240	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-trifluoromethyl-benzyl)-oxalamide	

Table 4

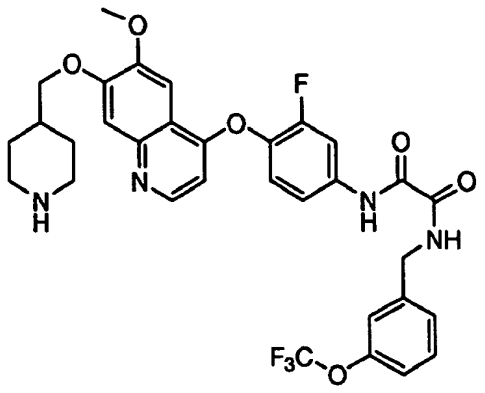
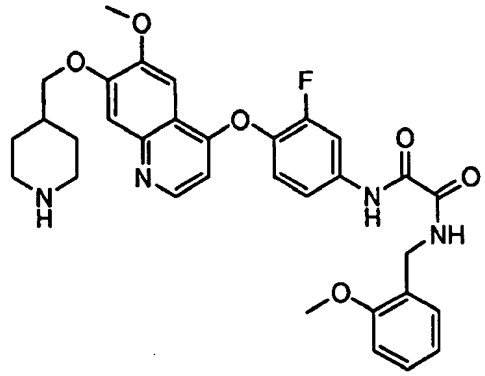
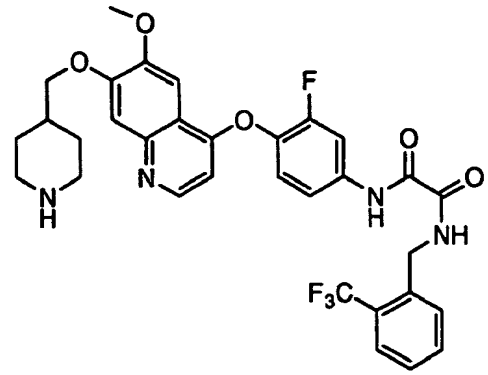
Entry	Name	Structure
241	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-trifluoromethoxy-benzyl)-oxalamide	
242	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-methoxy-benzyl)-oxalamide	
243	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-trifluoromethyl-benzyl)-oxalamide	

Table 4

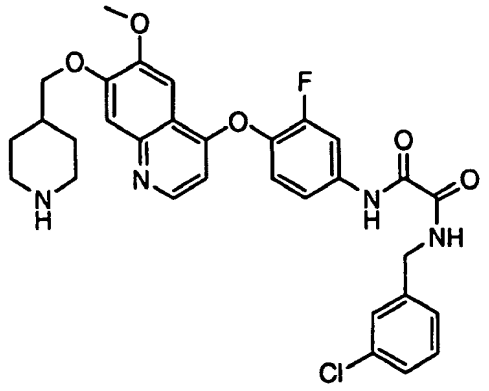
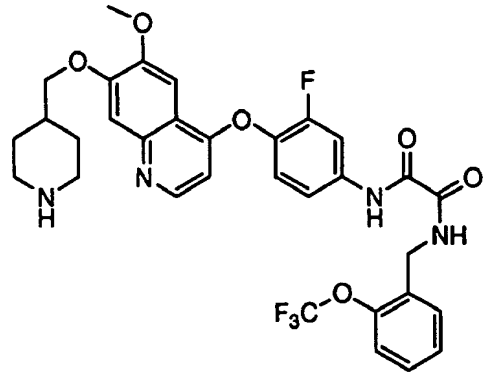
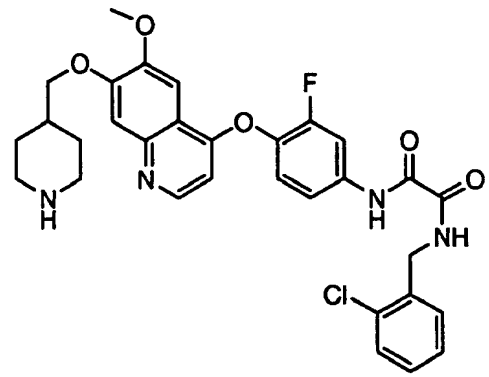
Entry	Name	Structure
244	N-(3-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
245	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-trifluoromethoxy-benzyl)-oxalamide	
246	N-(2-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 4

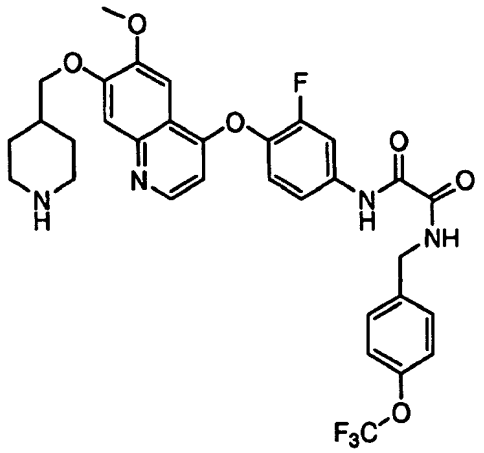
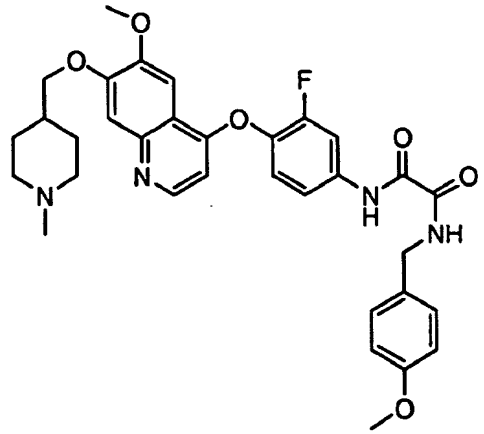
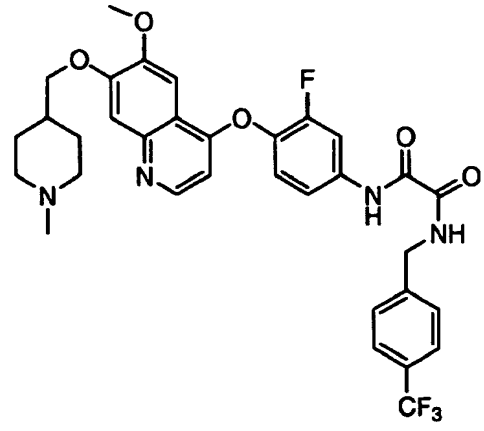
Entry	Name	Structure
247	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethoxy-benzyl)-oxalamide	
248	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-methoxy-benzyl)-oxalamide	
249	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(4-trifluoromethyl-benzyl)-oxalamide	

Table 4

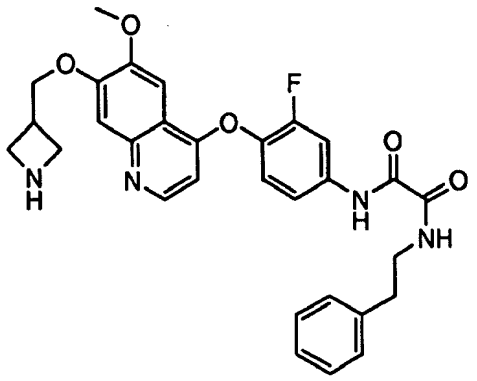
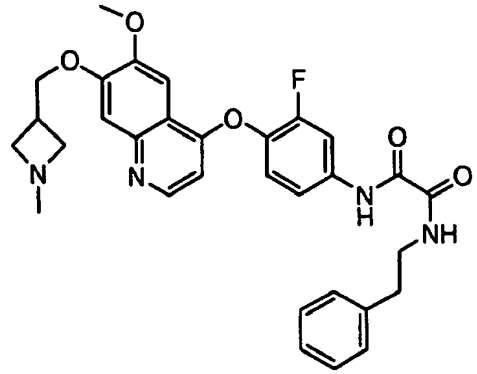
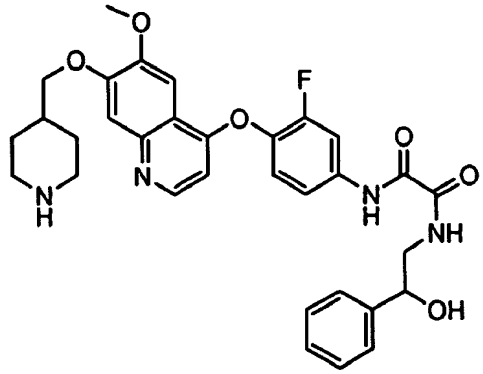
Entry	Name	Structure
250	N-{4-[7-(Azetidin-3-ylmethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-N'-phenethyl-oxalamide	
251	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-azetidin-3-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
252	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-hydroxy-2-phenyl-ethyl)-oxalamide	

Table 4

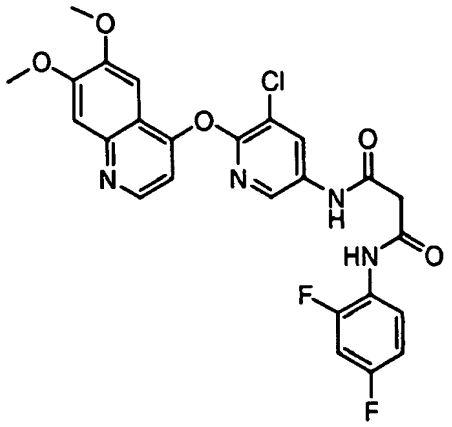
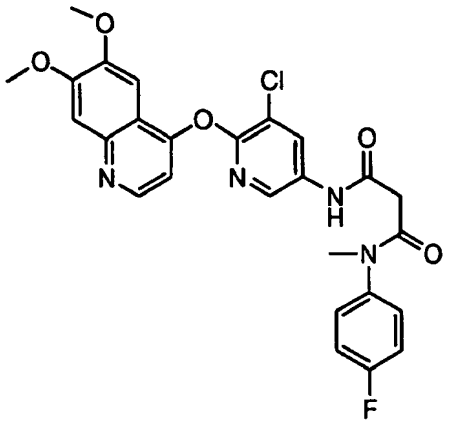
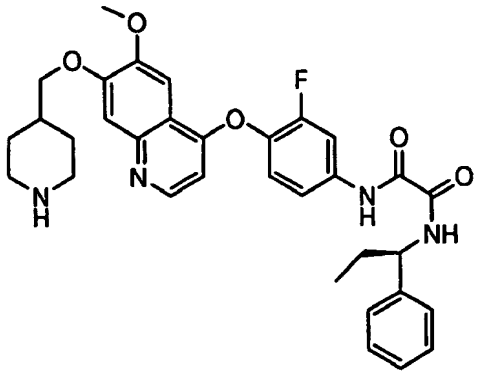
Entry	Name	Structure
253	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(2,4-difluoro-phenyl)-malonamide	
254	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(4-fluoro-phenyl)-N'-methyl-malonamide	
255	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R-phenyl-propyl)-oxalamide	

Table 4

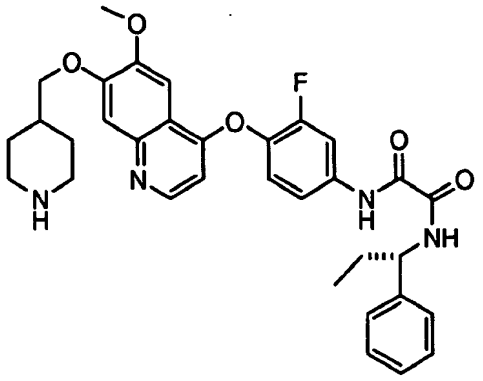
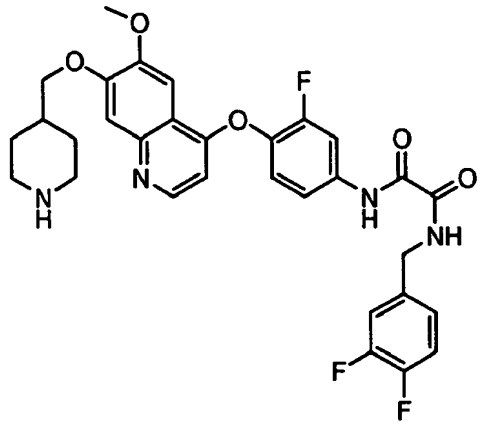
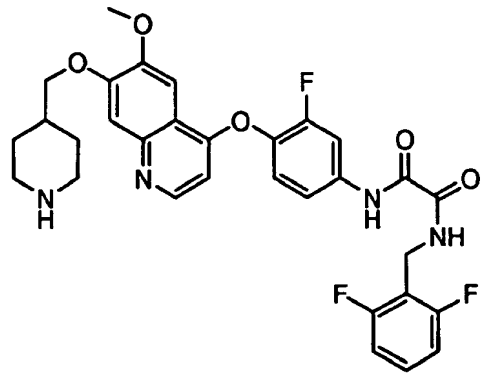
Entry	Name	Structure
256	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(1R-phenyl-propyl)-oxalamide	
257	N-(3,4-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
258	N-(2,6-Difluoro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 4

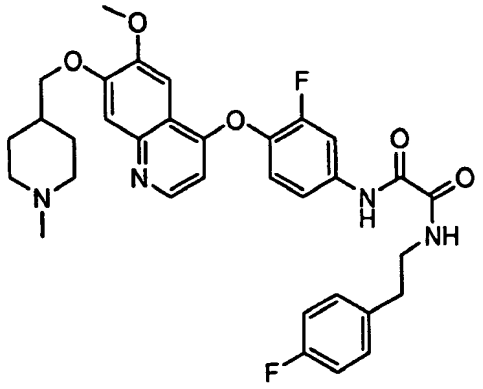
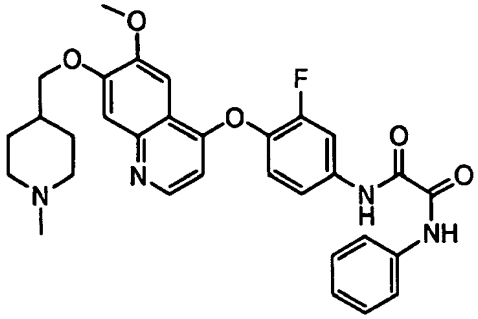
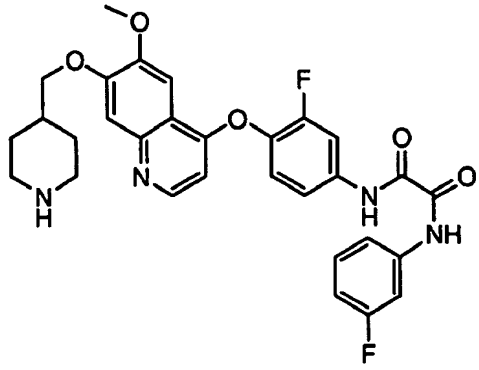
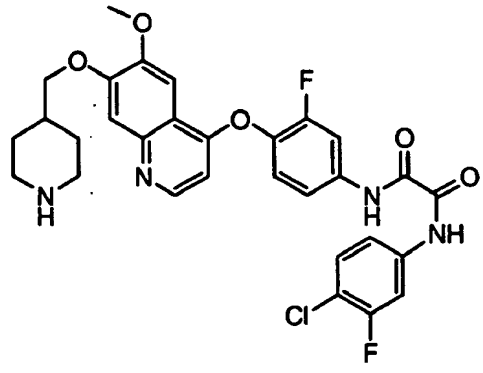
Entry	Name	Structure
259	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[2-(4-fluoro-phenyl)-ethyl]-oxalamide	
260	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-phenyl-oxalamide	
261	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-fluoro-phenyl)-oxalamide	
262	N-(4-Chloro-3-fluoro-phenyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 4

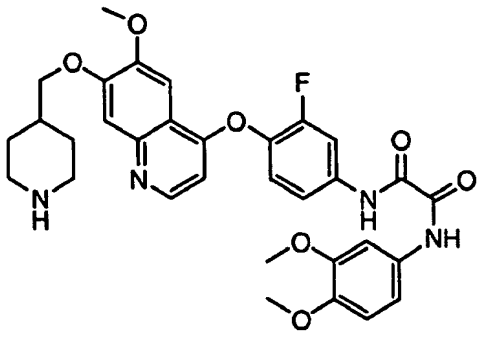
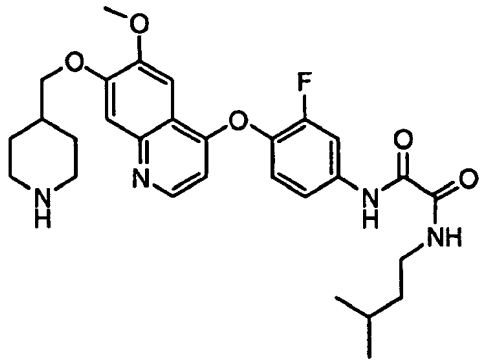
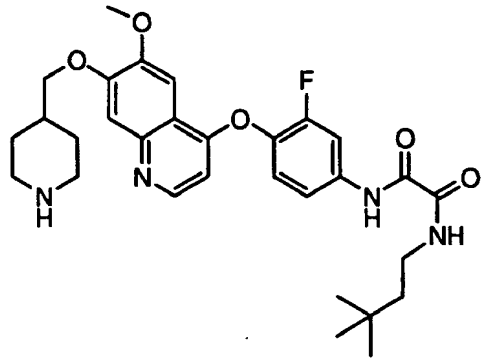
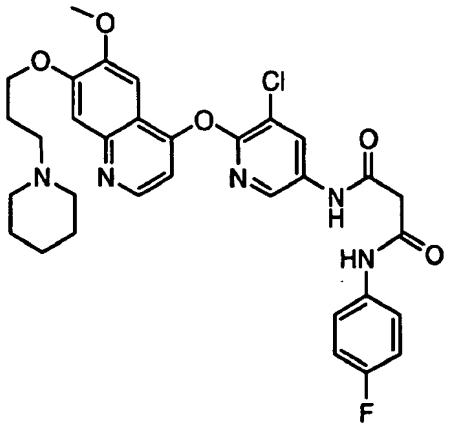
Entry	Name	Structure
263	N-(3,4-Dimethoxy-phenyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
264	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(3-methyl-butyl)-oxalamide	
265	N-(3,3-Dimethyl-butyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
266	N-{5-Chloro-6-[6-methoxy-7-(3-piperidin-1-yl-propoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	

Table 4

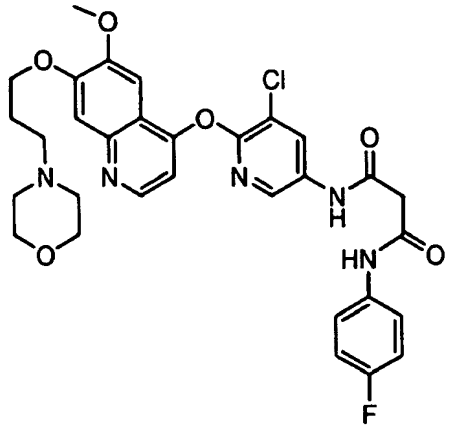
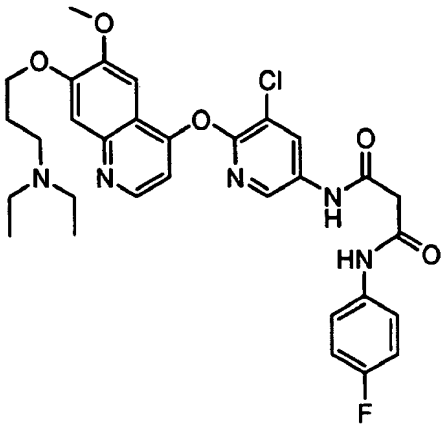
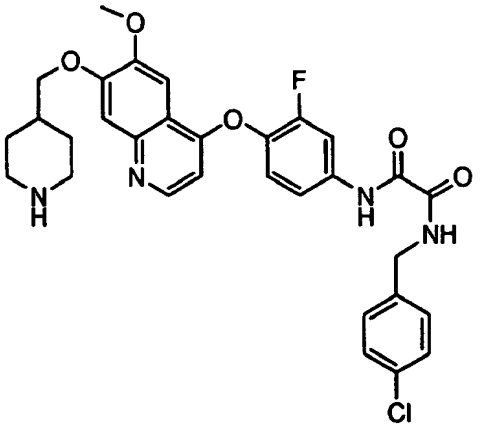
Entry	Name	Structure
267	N-{5-Chloro-6-[6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	
268	N-{5-Chloro-6-[7-(3-diethylamino-propoxy)-6-methoxy-quinolin-4-yloxy]-pyridin-3-yl}-N'-(4-fluoro-phenyl)-malonamide	
269	N-(4-Chloro-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 4

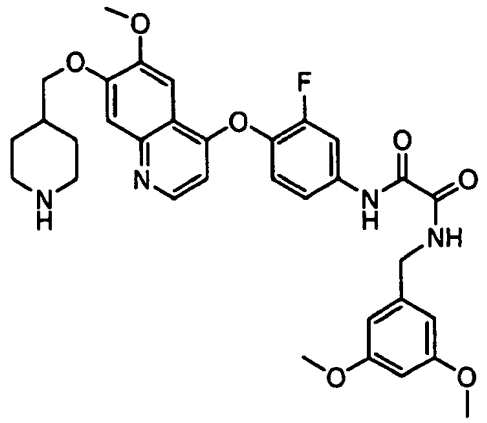
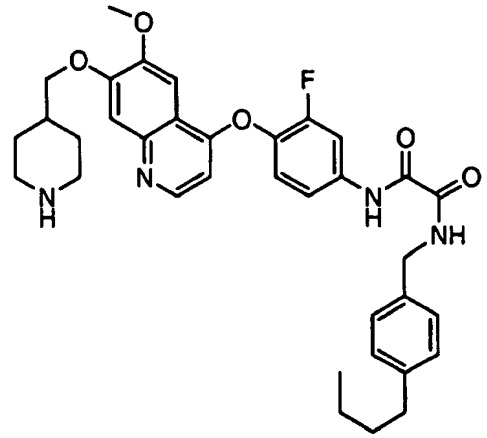
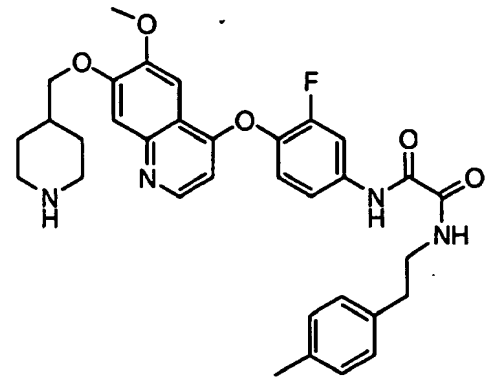
Entry	Name	Structure
270	N-(3,5-Dimethoxy-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
271	N-(4-Butyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
272	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-p-tolyl-ethyl)-oxalamide	

Table 4

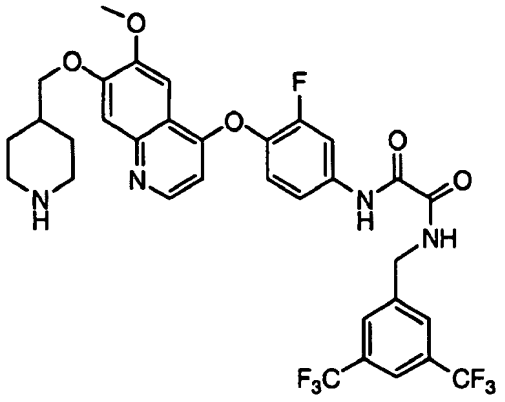
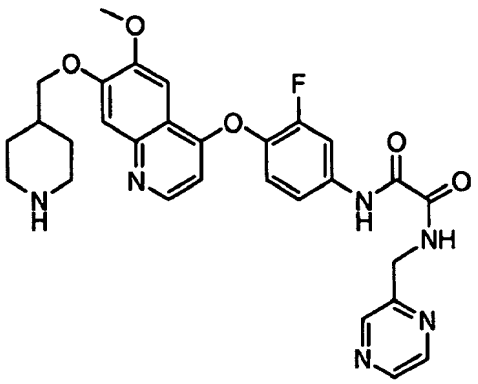
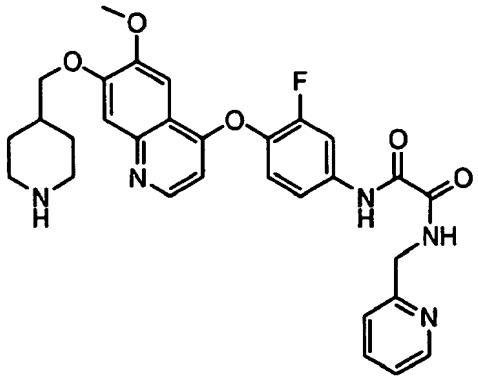
Entry	Name	Structure
273	N-(3,5-Bis-trifluoromethyl-benzyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
274	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-pyrazin-2-ylmethyl-oxalamide	
275	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-pyridin-2-ylmethyl-oxalamide	

Table 4

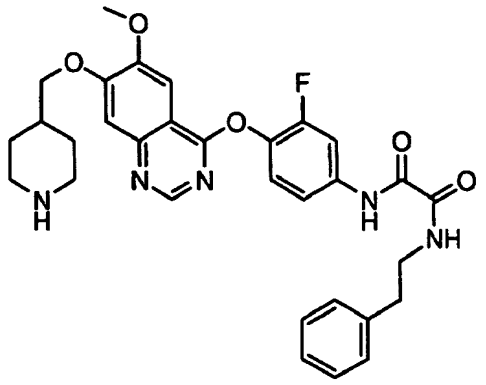
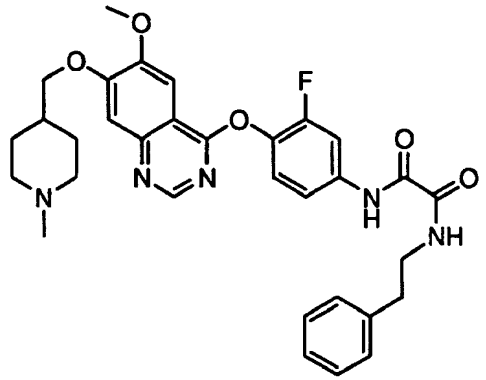
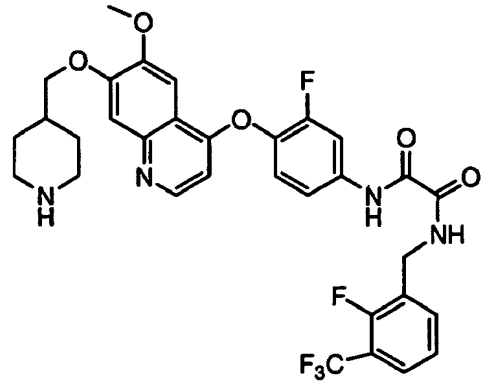
Entry	Name	Structure
276	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
277	N-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
278	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-fluoro-3-trifluoromethyl-benzyl)-oxalamide	

Table 4

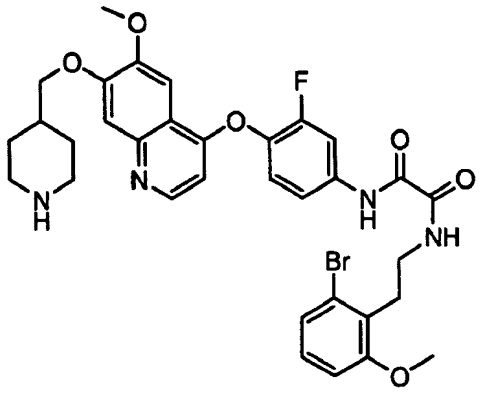
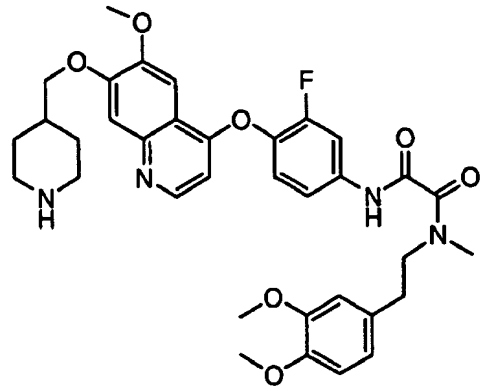
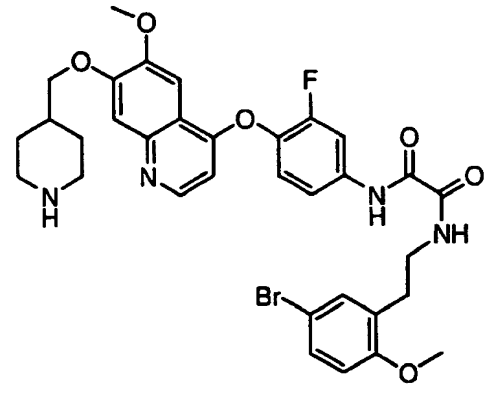
Entry	Name	Structure
279	N-[2-(2-Bromo-6-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
280	N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N-methyl-oxalamide	
281	N-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 4

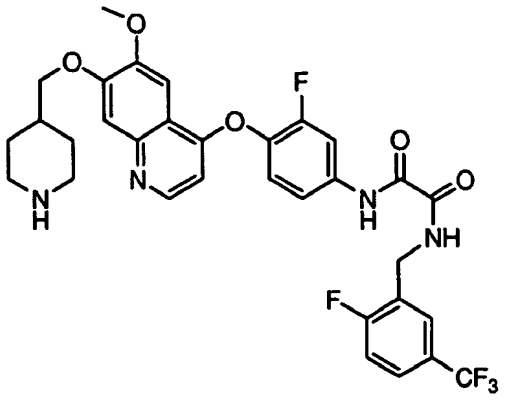
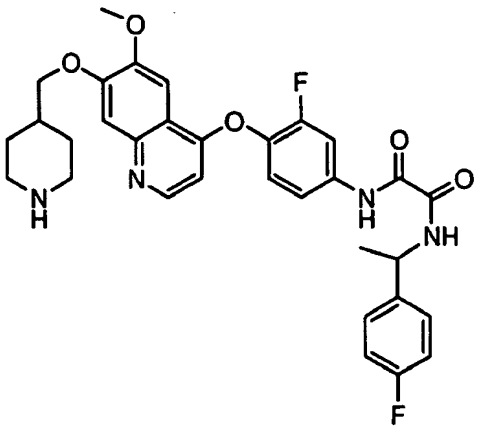
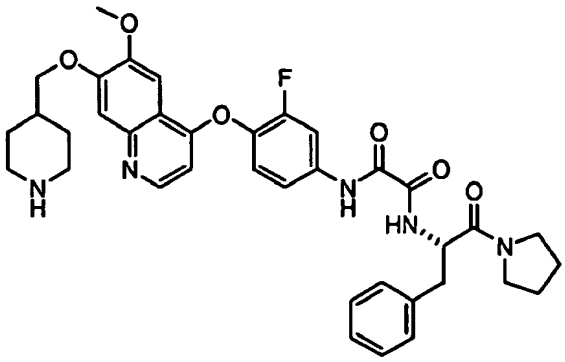
Entry	Name	Structure
282	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-fluoro-5-trifluoromethyl-benzyl)-oxalamide	
284	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-[1-(4-fluoro-phenyl)-ethyl]-oxalamide	
285	N-(1S-Benzyl-2-oxo-2-pyrrolidin-1-yl-ethyl)-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 4

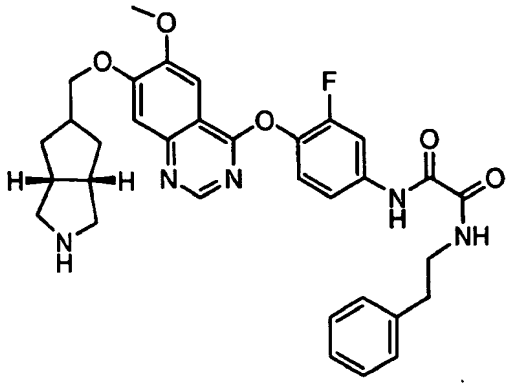
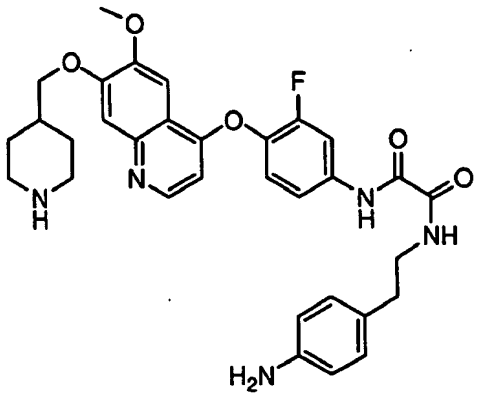
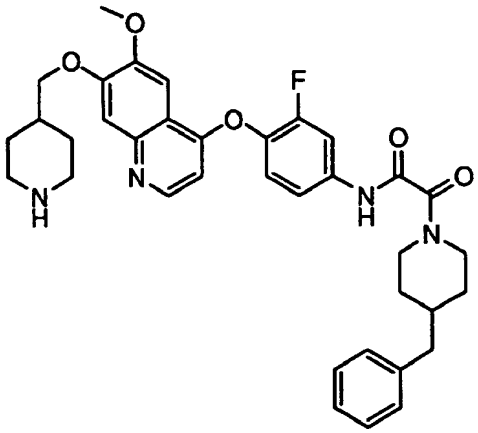
Entry	Name	Structure
286	N-{3-Fluoro-4-[6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-N'-phenethyl-oxalamide	
287	N-[2-(4-Amino-phenyl)-ethyl]-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
288	2-(4-Benzyl-piperidin-1-yl)-N-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-acetamide	

Table 4

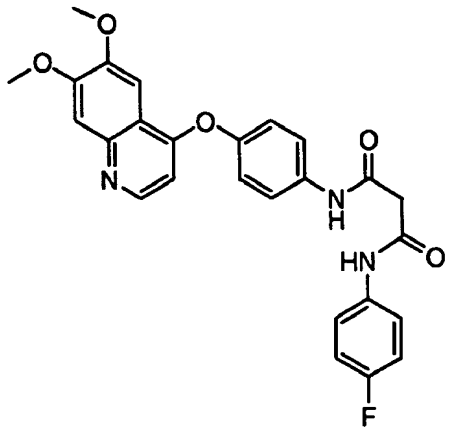
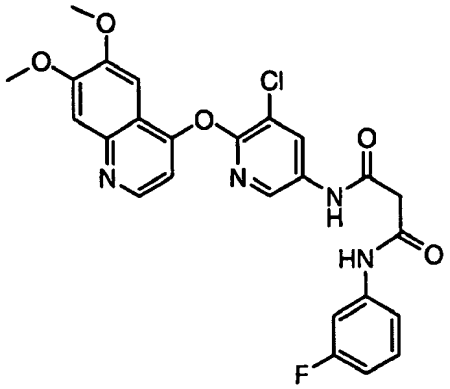
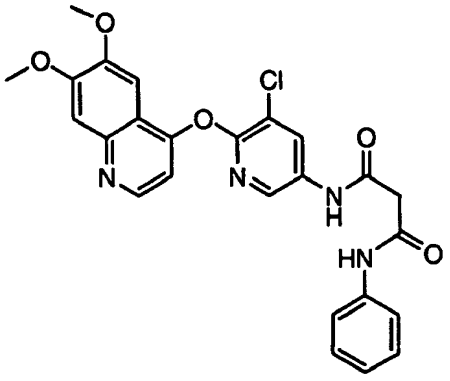
Entry	Name	Structure
289	N-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenyl]-N'-(4-fluoro-phenyl)-malonamide	
291	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(3-fluoro-phenyl)-malonamide	
292	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-phenyl-malonamide	

Table 4

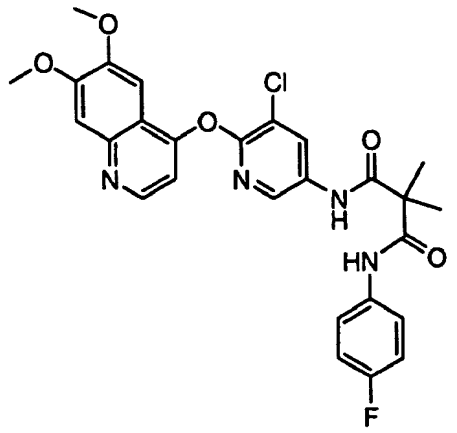
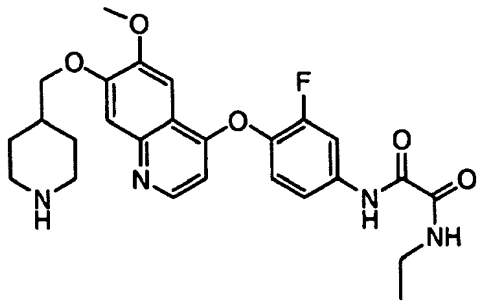
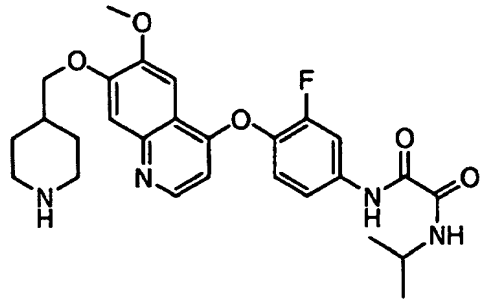
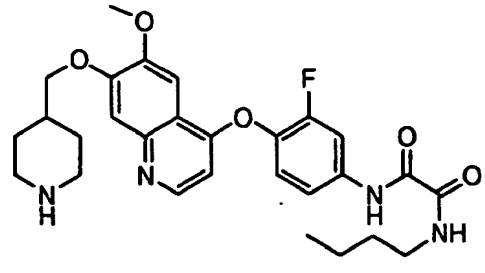
Entry	Name	Structure
293	N-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-N'-(4-fluoro-phenyl)-2,2-dimethyl-malonamide	
294	N-Ethyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
295	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-isopropyl-oxalamide	
296	N-Butyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	

Table 4

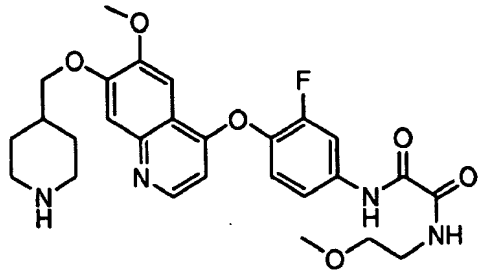
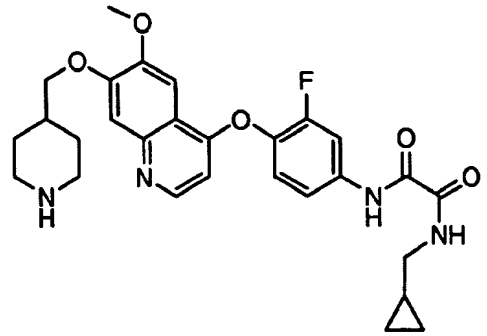
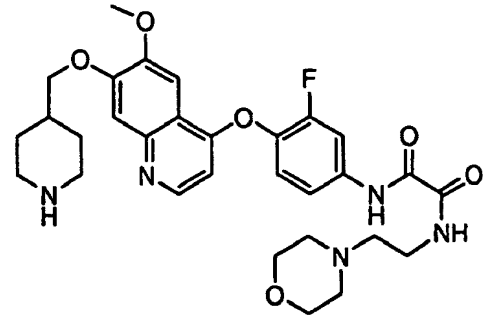
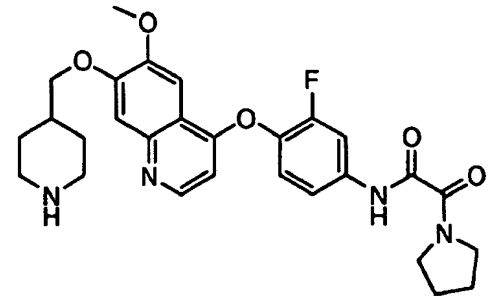
Entry	Name	Structure
297	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-methoxy-ethyl)-oxalamide	
298	N-Cyclopropylmethyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide	
299	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N'-(2-morpholin-4-yl-ethyl)-oxalamide	
300	N-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-pyrrolidin-1-yl-acetamide	

Table 4

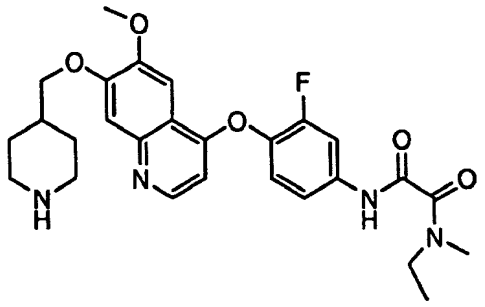
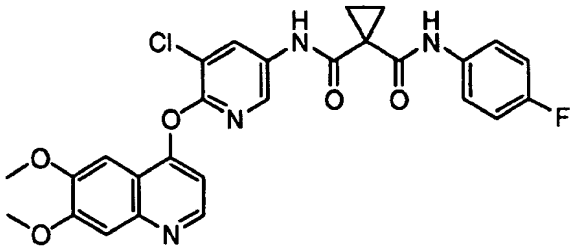
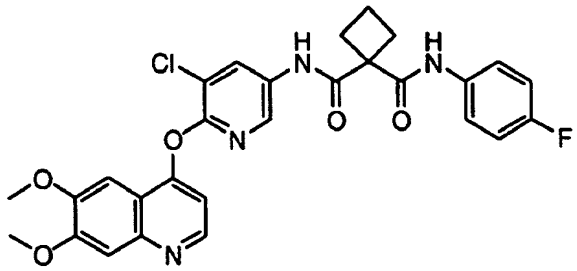
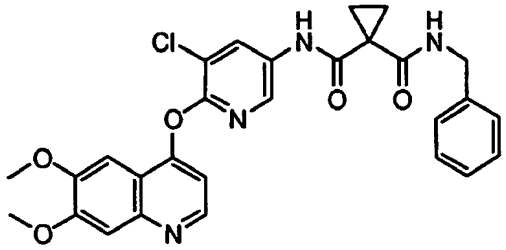
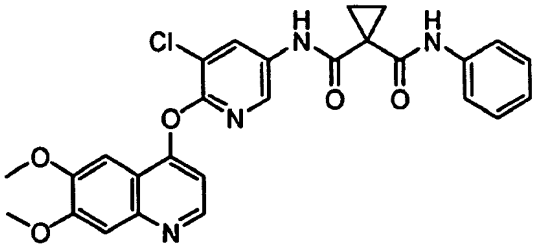
Entry	Name	Structure
301	N-Ethyl-N'-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-N-methyl-oxalamide	
302	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
303	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
304	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(phenylmethyl)cyclopropane-1,1-dicarboxamide	
305	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-phenylcyclopropane-1,1-dicarboxamide	

Table 4

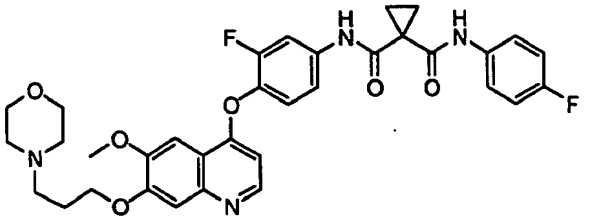
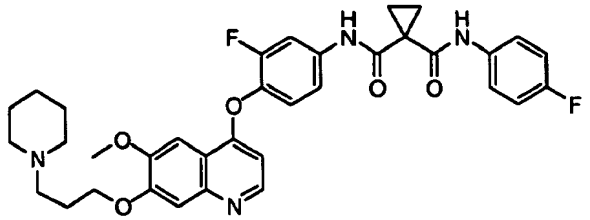
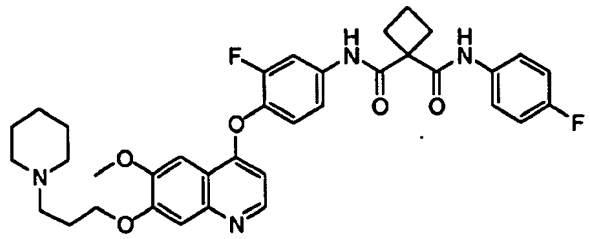
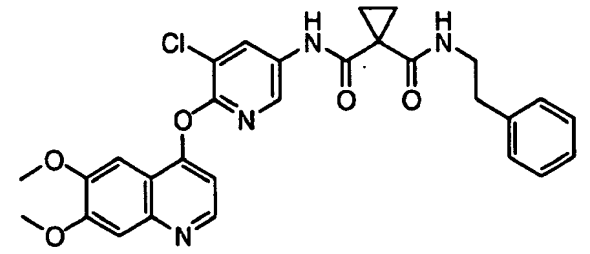
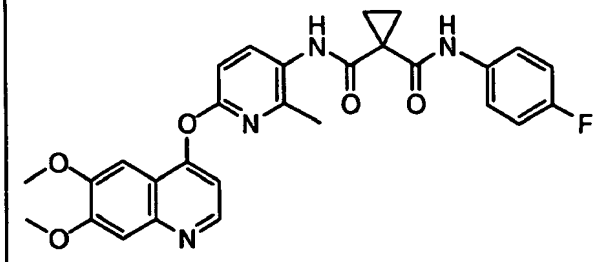
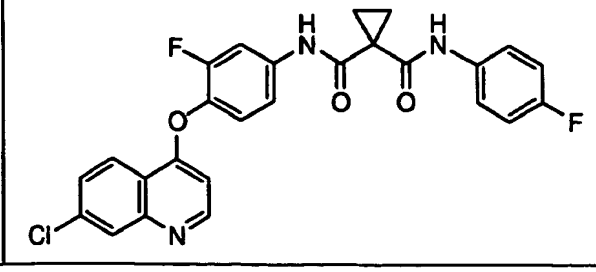
Entry	Name	Structure
306	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
307	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
308	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
309	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-N'-(2-phenylethyl)cyclopropane-1,1-dicarboxamide	
310	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
311	N-{4-[(7-chloroquinolin-4-yl)oxy]-3-fluorophenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 4

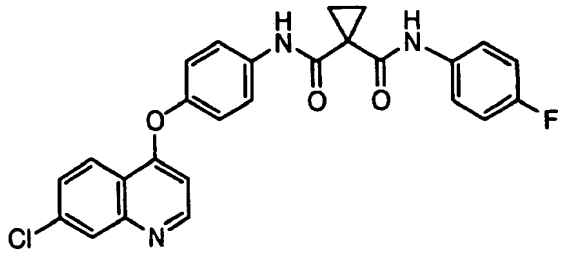
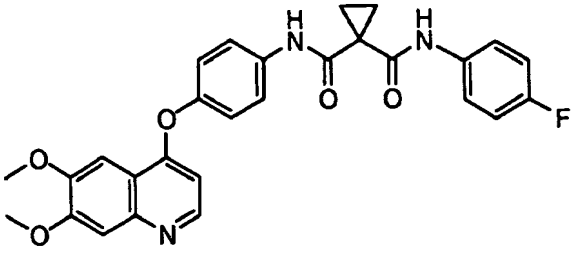
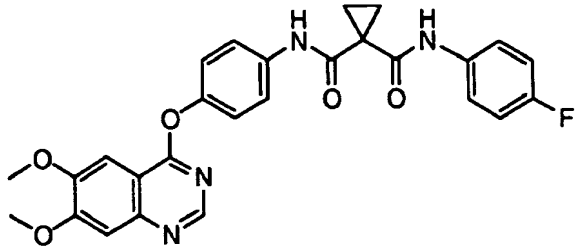
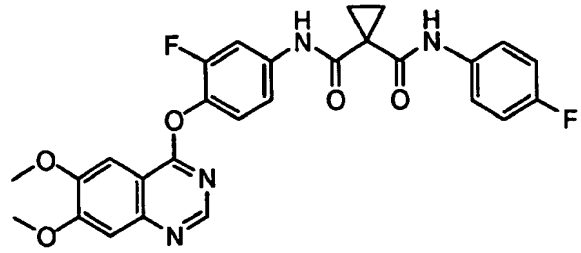
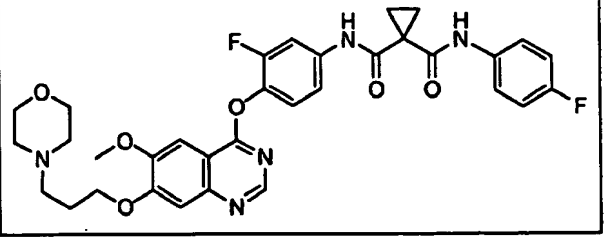
Entry	Name	Structure
312	N-{4-[(7-chloroquinolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
313	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
314	N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
315	N-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
316	N-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 4

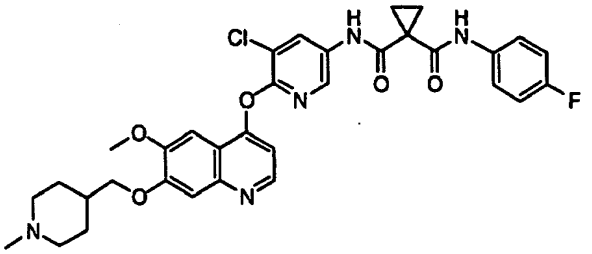
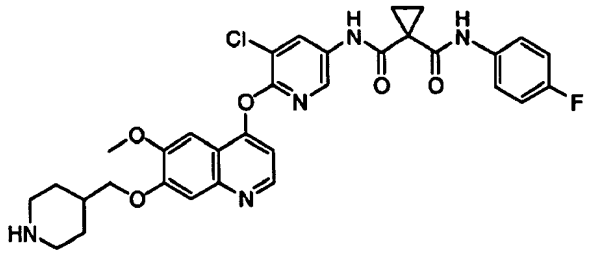
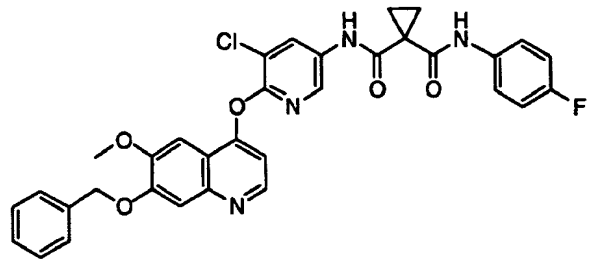
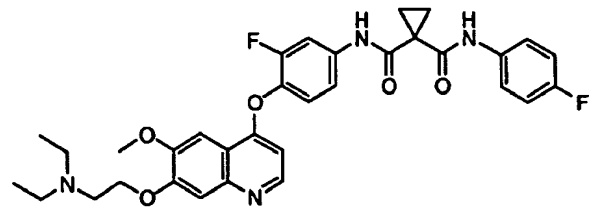
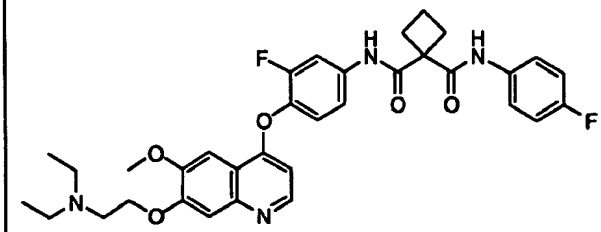
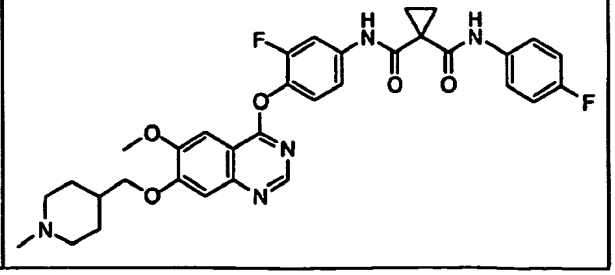
Entry	Name	Structure
317	N-{5-chloro-6-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]pyridin-3-yl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
318	N-[5-chloro-6-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
319	N-[5-chloro-6-({6-(methyloxy)-7-[(phenylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
320	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
321	N-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide	
322	N-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 4

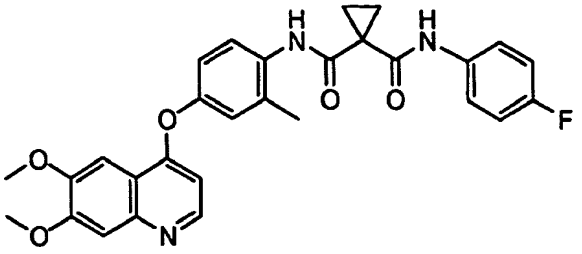
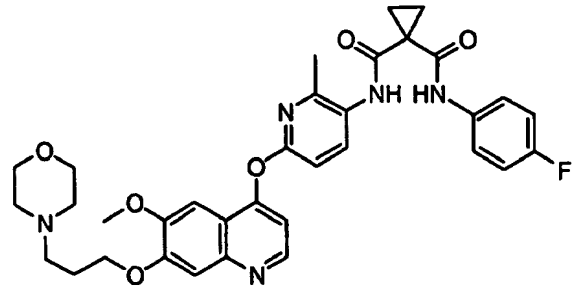
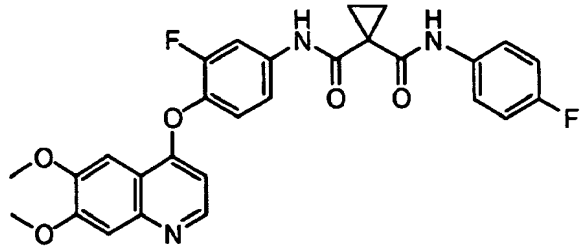
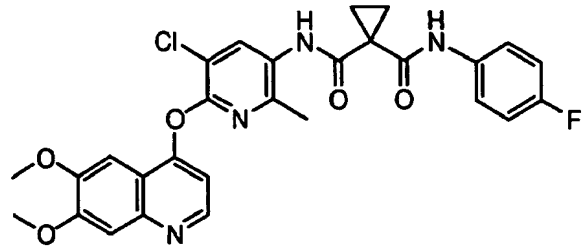
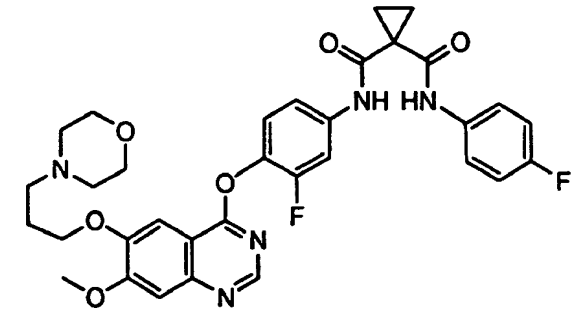
Entry	Name	Structure
323	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
324	N-(4-fluorophenyl)-N'-[2-methyl-6-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]cyclopropane-1,1-dicarboxamide	
325	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
326	N-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloro-2-methylpyridin-3-yl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
327	N-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 4

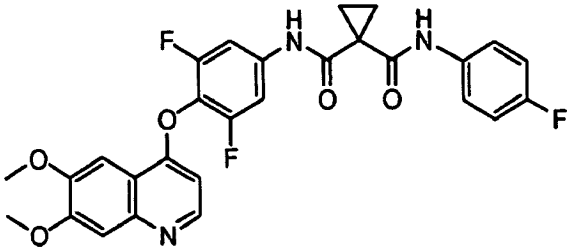
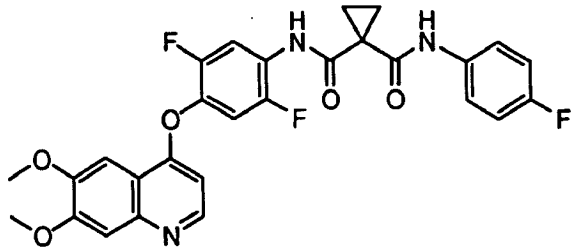
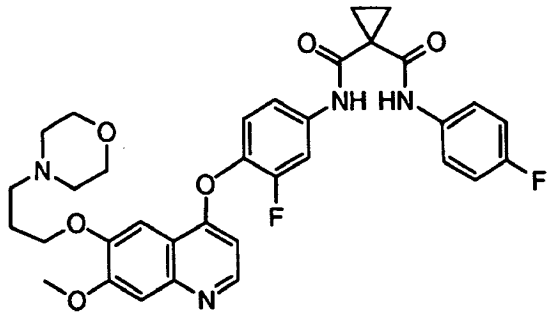
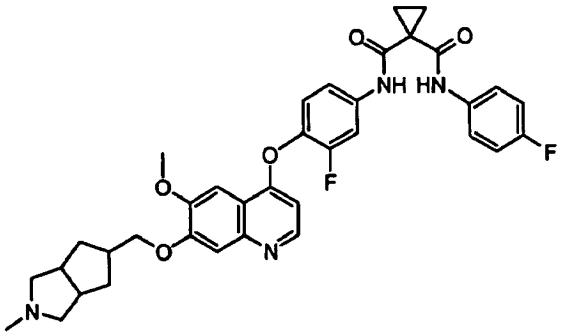
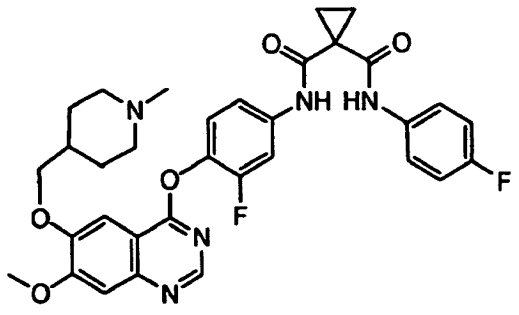
Entry	Name	Structure
328	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3,5-difluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
329	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,5-difluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
330	N-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
331	N-{3-fluoro-4-[(6-(methyloxy)-7-(2-methyl octahydrocyclopenta[c]pyrrol-5-ylmethoxy)quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
332	N-{3-fluoro-4-[(7-(methyloxy)-6-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 4

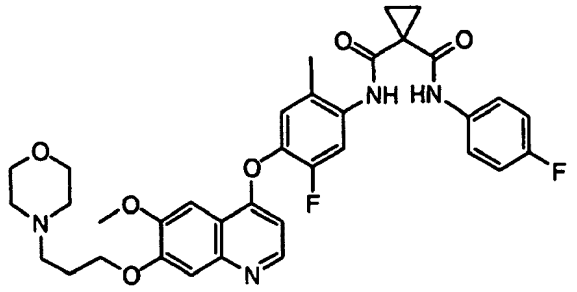
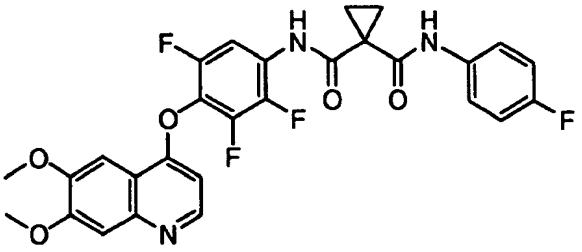
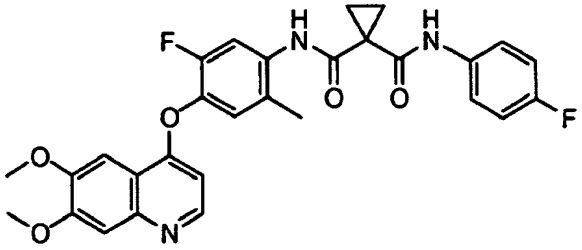
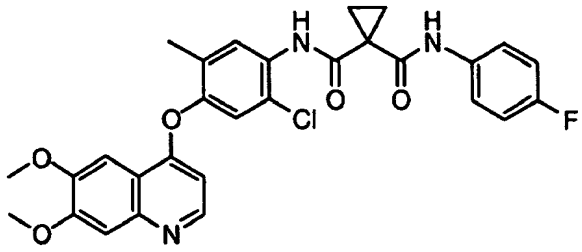
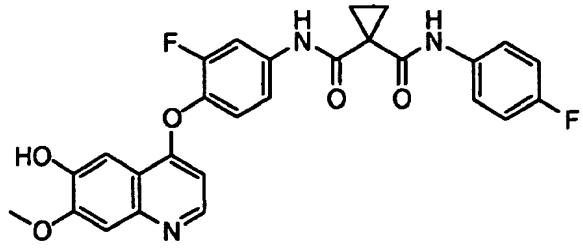
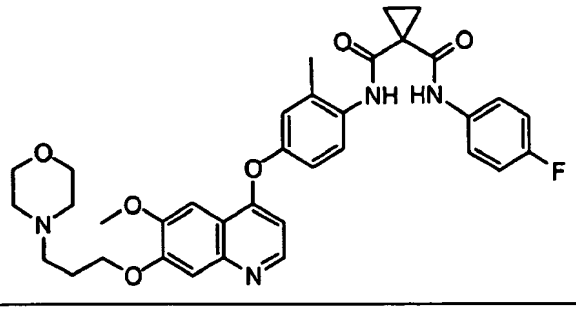
Entry	Name	Structure
333	N-[5-fluoro-2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
334	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,3,5-trifluorophenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
335	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-2-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
336	N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-methylphenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	
337	N-(3-fluoro-4-{[6-hydroxy-7-(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide	

Table 4

Entry	Name	Structure
338	N-(4-fluorophenyl)-N'-[2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide	

53. The process according to any of claims 1 - 52, further comprising converting said compound to a pharmaceutically acceptable salt, hydrate, or prodrug thereof.

ABSTRACT

The present invention provides methods for making compounds for modulating protein kinase enzymatic activity for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration and chemoinvasion. More specifically, the invention provides processes for making quinazolines and quinolines which inhibit, regulate and/or modulate kinase receptor, particularly c-Met, KDR, c-Kit, flt-3 and flt-4, signal transduction pathways related to the changes in cellular activities as mentioned above, and compositions which contain these compounds.

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